Pest Management Regulatory Agency
Agence de réglementation de la lutte antiparasitaire

Regulatory Note

REG99-02

Diflufenzopyr

The active ingredient diflufenzopyr and the formulated product Distinct®, containing diflufenzopyr and dicamba for the control of specific broadleaf weeds in field corn in Eastern Canada, have been granted Section 17 temporary registrations.

This regulatory note provides a summary of data reviewed and the rationale for the regulatory decision concerning these products.

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Foreword

Health Canada's Pest Management Regulatory Agency (PMRA) and the United States (U.S.) Environmental Protection Agency (EPA) have simultaneously issued limited term registrations for Distinct®, a herbicide developed by BASF Corp. for use on field corn. Distinct® herbicide, which contains the active ingredients diflufenzopyr and dicamba, is effective against annual broadleaf weeds such as redroot pigweed, lamb's-quarters, common ragweed, wild buckwheat, lady's thumb and velvetleaf. The product will be sold and used for the first time in both the U.S. and Canada during the 1999 growing season.

Distinct® is classed as a reduced-risk chemical pesticide, as it presents lower risks to human health than traditional chemical pesticides. The use pattern for the product, e.g., rates, timing and frequency of application, is parallel in both countries, providing a level playing field that promises greater fairness to growers. A parallel use pattern also allows for harmonized maximum residue limits (MRLs) or tolerances, which are key to avoiding trade irritants.

Based on a review of efficacy data, the U.S. label provides for slightly higher use rates to cover certain weed species such as hemp dogbane, silverleaf nightshade, spotted knapweed, shattercane and broadleaf signal grass, which are not considered commercially important in Canada and not claimed on the Canadian label. There was a reduction of 33 percent from the original Canadian label proposals for Distinct® applied at the spike and early post-emerge stage of the crop. This represents a substantial reduction in potential environmental and human exposure, as well as an opportunity for cost savings to users.

Only limited quantities of diflufenzopyr are expected to be used during the 1999 crop year. BASF will be carrying out additional environmental studies as a condition of this temporary registration.

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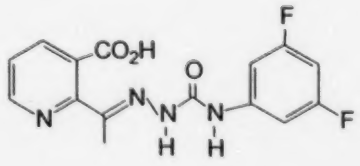
1.0 The active substance, its properties, uses, proposed classification and labelling

1.1 Identity of the active substance and preparation containing it

Active substance:	diflufenzopyr
Function:	herbicide
Chemical name (International Union of Pure and Applied Chemistry):	2-{1-[1-(3,5-difluorophenyl)semicarbazono]ethyl} nicotinic acid
Chemical name (Chemical Abstracts Service [CAS]):	2-[1-[[[(3,5-difluorophenyl)amino]carbonyl] hydrazono]ethyl]-3-pyridinecarboxylic acid
CAS Registry Number:	109293-97-2
Nominal purity of active:	99.1%
Identity of relevant impurities of toxicological, environmental and/or other significance:	Impurities of toxicological concerns are not expected to be present in the raw materials, nor are they expected to be generated during the manufacturing process.
Molecular Formula:	$C_{15}H_{12}N_4O_3F_2$
Molecular Mass:	334.28
Structural Formula:	

1.2 Physical and chemical properties of active substance

Table 1.1 Technical product: Diflufenzopyr acid (BAS 654 H or SAN 835 H)

Property	Result	Comment
Colour and physical state	Off-white solid	Not applicable (N/A)
Odour	None	N/A
Melting point/range	135.5°C, decomposes before 155°C	N/A
Boiling point/range	N/A	N/A
Tap density	0.24 g/mL at 25°C	N/A
pH at 25°C	3.9	N/A
Vapour pressure at 20 and 25°C	$<1 \times 10^{-7}$ mm Hg ($<1.33 \times 10^{-5}$ Pa)	Relatively non-volatile under field conditions. Low potential for residues to decrease as a result of volatilization.
UV/visible absorption spectrum in water	λ nm / ε (L/mol-cm) 234.1 / 1.98×10^4 294.5 / 1.43×10^4 No ε at λ >350 nm	Phototransformation will not be a major route of transformation.
Solubility in water at 25°C	pH / Solubility (parts per million [ppm]) Reagent / 63 ± 13 5.0 / 270 ± 27 7.0 / 5850 ± 98 9.0 / 10,546 ± 131	Highly soluble in water at neutral pH; a potential for surface runoff and leaching.
Henry's Law Constant	7.06×10^{-5} to 7.6×10^{-7} Pa m^3 /mole	Indicates a negligible potential for volatilization from water or moist soil.
Solvent solubility (mg/L)	Solvent / Solubility (mg/L) tetrahydro-furan / 30,000 hexane / not detected (ND) i-PrOH / 922 DMSO / 248,000 $MeCl_2$ / 12.1 ACN / 228 acetone / 3360 toluene / 1.15	Soluble in polar organic solvents.

Property	Result	Comment
Octanol/water partition coefficient (K_{ow})	pH 5.0 → K_{ow} 2.76 7.0 → 0.34 9.0 → 0.17	Will not bioaccumulate in biological tissue.
Dissociation constant (pK_a)	pK_a = 3.18	Predominates as an anion at acidic, neutral and basic pH; no significant effects on adsorption resulting from pH of soil in the range of values found in Canada.
Stability (temperature, metals)	Technical grade active ingredient (TGAI) is unstable in the presence of metals and in sunlight. Recoveries after contact with iron, copper, aluminum, Fe^{+2}, Cu^{+2} and Al^{+3} ions for 28 days (d) at 25°C were 2.0, 3.1, 5.1, 21.5, 88.0 and 98.0% respectively. Photolysis $t_{1/2}$ of TGAI at pH 7 and 25°C was 54.1 d.	N/A

Table 1.2 End-use product: Distinct® (BAS 662H 70WG)

Property	Result	Comment
Colour	Grey	N/A
Odour	Moderate, neutral, unpleasant odour	N/A
Physical state	Solid powder	N/A
Formulation type	Wettable powder	N/A
Guarantee	Diflufenzopyr at 20% and dicamba at 50% (both present as sodium salt)	N/A
Container material and description	High density polypropropylene jug. Future package may include a gable top carton container with paper polymer-laminated surface.	N/A
Tap density	0.6 g/mL	N/A
pH of 1% dispersion in water at 25°C	8.51	N/A
Oxidizing or reducing action	Showed no reactivity with $KMnO_4$, Zn, most organic solvents and ammonium phosphate monobasic.	N/A

Property	Result	Comment
Storage stability	Stable for two years (yr) in glass containers at room temperature. Results before and after storage were within ± 0.2%.	N/A
Corrosive characteristics	Corrodes C1020 type steel at <0.0001 mm/yr at 55°C.	N/A
Explodability	The product is not impact-explosive sensitive.	N/A
Surfactants	Reax 910 (Lignosulfonic acid, sodium salt) and Morwet (anionic)	Increased absorption expected

1.3 Details of uses and further information

Diflufenzopyr is a semicarbazone herbicide. Diflufenzopyr is classified as a Group 4 herbicide in which the mode of action is auxin transport inhibition. Diflufenzopyr will be commercialized as a premix product with dicamba, an active ingredient (a.i.) that is currently registered in Canada. The commercial name for the diflufenzopyr + dicamba product is Distinct®. Distinct® contains 20% diflufenzopyr and 50% dicamba providing an overall guarantee of 70% a.i. Distinct® is marketed in plastic bags.

Distinct® may be used for pre-emergent, spike stage (spike to one leaf), early post-emergent (two to three leaf) and late post-emergent (four to six leaf) application on field corn in Eastern Canada. Distinct® is not for use on sweet corn or seed corn. An application of Distinct® at the above-stated timings relative to the crop, except for pre-emergent where the tankmix with dimethenamid is recommended, is effective in controlling the following broadleaf weeds: redroot pigweed, common ragweed, lamb's-quarters, wild buckwheat, lady's thumb and velvetleaf (velvetleaf controlled with post-emergent application only).

Distinct® is to be applied at a rate of 285 g/ha (200 g a.i./ha) with ground equipment only. When applied at the early or late post-emergent treatment, a non-ionic surfactant at 0.25% volume ratio (v/v) and liquid urea ammonium nitrate at 1.25% v/v must be used. Distinct® may be applied a maximum of once per year. Corn may be harvested or grazed once the crop has reached the early dent stage or later. This corresponds to 82 d after emergence.

Distinct® can be tankmixed with dimethenamid at a rate of 1.125 kg a.i./ha for control of the above broadleaf weeds in addition to the following annual grass weeds: green foxtail, yellow foxtail, crabgrass (smooth and large), old witchgrass, barnyard grass and fall panicum.

2.0 Methods of analysis

2.1 Methods for analysis of the active substance as manufactured

Two isocratic high performance liquid chromatography (HPLC) methods were used for the determination of the active substance and significant impurities (content ≥0.1%) in the technical product. The methods have been shown to have satisfactory specificity, linearity, precision and accuracy.

2.2 Method for formulation analysis

A solvent gradient HPLC was used for the determination of active substance in the formulation. The method has been shown to have satisfactory specificity, linearity, precision and accuracy.

2.3 Methods for residue analysis

2.3.1 Multi-residue methods for residue analysis

Diflufenzopyr metabolite, 8-hydroxymethyl-5(6H)-pyrido[2,3-d]pyridazinone (8-hydroxymethyl-M1) (M10), was tested using a U. S. Food and Drug Administration multi-residue method. However, neither diflufenzopyr nor another metabolite, 8-methyl-5-hydroxy-pyrido(2,3-d)-pyridazine (phthalazinone) (M1), was detected.

2.3.2 Methods for residue analysis of plants and plant products

The residue of concern (ROC) for corn raw agricultural commodities (RAC) was defined from the corn metabolism study as the parent compound and its metabolites convertible to M1 and expressed in diflufenzopyr equivalent.

For corn commodities, the gas chromatography (GC) method (Sandoz Agro Method AM-0966-0995-0) converted the parent compound to M1 and measured residues of diflufenzopyr and M1. Quantification was performed with a GC/nitrogen-phosphorous detector (NPD) or GC/mass selective detection (MSD). The limit of quantitation (LOQ) is 0.01 ppm, based on M1. Since the molecular weight of M1 is roughly half of the parent compound, the concentration of M1 determined must be doubled when expressed in diflufenzopyr equivalent (i.e., 0.02 ppm LOQ).

The EPA indicated that Method AM-0966-0995-0 was suitable as an enforcement method for diflufenzopyr. However, the petitioner requested a GC/mass spectrometry (MS) method, BASF Method D9709, to replace AM-0966-0995-0 as the enforcement method. This method also converted the parent compound to M1. The LOQ for the parent compound was 0.05 ppm. The EPA laboratories are validating this method.

2.3.3 Methods for residue analysis of food of animal origin

No analytical method was submitted for livestock. Based on animal metabolism studies, residues of diflufenzopyr are unlikely to be detectable in meat, milk and eggs as a result of feeding treated corn seeds or by-product. Therefore, an analytical method for the analysis of food of animal origin is not required.

3.0 Impact on human and animal health

3.1 Effects having relevance to human and animal health arising from exposure to the active substance or to impurities in the active substance or to their transformation products.

3.1.1 Absorption, distribution, metabolism and excretion

Male and female Wistar rats received either a single low intravenous dose (1.0 mg/kg body weight [bw]), single low oral dose (10.0 mg/kg bw), single high oral dose (1000 mg/kg bw) or 15 daily low oral doses (10.0 mg/kg bw) of diflufenzopyr, purity 98%, 10 or 15 rats per sex per group. Diflufenzopyr was radiolabelled as [phenyl-U-^{14}C] or [pyridinyl-4, 6-^{14}C]. Prior to dosing, five rats per sex in all but the repeat dose group were bile-duct cannulated, and sacrificed 48 hours (h) post-dosing. Of the remaining 10 rats per sex in each group (i.e., non-cannulated), five per sex per group were sacrificed 24 h post-dosing, and the remaining five per sex per group were sacrificed 72 h post-dosing.

[^{14}C]Diflufenzopyr was only partially absorbed from the gastrointestinal tract of orally dosed rats as indicated by the levels of excretion in urine and bile. In all orally dosed groups, 20–44% of the dose was excreted in the urine and 3–11% was excreted in the bile. In contrast, intravenously dosed rats excreted 61–89% of the dose in urine and 4–19% of the dose in bile. For all orally dosed groups, the level of absorption was similar between sexes. Dose level and pre-treatment had little effect on the proportion of the dose excreted in urine following oral administration.

Enterohepatic circulation plays a role in the elimination of [^{14}C]diflufenzopyr in rats; 3–19% of the dose was recovered in the bile of all dose groups.

Within 72 h of dosing, intravenously-dosed rats excreted the majority of radioactivity in urine (61–89%), whereas orally dosed rats excreted most of the radioactivity in feces (49–79%), regardless of radiolabel or sex. Pre-treatment did not appear to affect the pattern of excretion. Bile-cannulated rats excreted lesser amounts in feces compared to non-cannulated rats; 3–19% of the dose was excreted in bile. The estimated half-lives of radiocarbon eliminated in urine and feces was 5.3–6.9 h for all single intravenous and oral dose groups, and 7.7–10.8 h for all repeat oral dose groups.

Total radioactive residues (TRRs) in tissues from rats in all dose groups were <3% of the administered dose. Total tissue residue levels were highest in rats sacrificed at 24 h post-

dose; residue levels were highest in blood, blood cell and serum for the phenyl-labelled groups, and in liver and kidney for the pyridinyl-labelled groups.

Blood residue levels for all dose groups were <1% of the administered dose at all sampling intervals through 72 h post-dose.

Thin-layer chromatography (TLC) and HPLC analyses were conducted on 0- to 72-h and 0- to 48-h urine and feces samples, and on 0- to 48-h bile samples from each treatment regimen. The structures of the metabolites were confirmed using 2-D TLC, HPLC, liquid chromatography (LC)/MS, DIP/MS, FAB/MS, and proton nuclear magnetic resonance. For each dose group, the metabolic profile was similar between sexes, except for differences in metabolite levels. Unchanged diflufenzopyr was identified as the major component in urine, feces, and bile from all dose groups using either radiolabel. Urinary metabolites identified in the ^{14}C-phenyl-labelled dose groups included 3,5-difluoroaniline (aniline) (M2) and 6-((3,5-difluorophenyl) carbamoyl)-8-methyl-pyrido (2,3-d)-5-pyridazinone (carbamoyl phthalazinone) (M5). Urinary metabolites identified in the ^{14}C-pyridinyl-labelled dose groups included M1; M5; 2-acetyl nicotinic acid (2-acetyl nicotinic acid) (M6); 8-methylpyrido[2,3-d]pyridazine-2,5(1H, 6H)-dione (2-keto-M1) (M9); M10; and 8-hydroxymethylpyrido[2,3-d]pyridazine-2,5(1H,6H)-dione (2-keto-8-hydroxymethyl-M1 or Metabolite E)(M19). Fecal metabolites identified in the phenyl label groups included methyl N-(3,5-difluorophenyl)carbamate (M8) and M5. Fecal metabolites identified in the pyridinyl label groups included M1, M5, M6, M9, and M10. Besides the parent compound, bile samples also contained minor amounts of M5 (both labels) and M1 (pyridinyl label only).

The data indicate that diflufenzopyr is excreted primarily unchanged in urine, feces and bile. Minor amounts of hydrolysis products (M1, M5 and M6) and hydroxylation products (M9, M10 and M19) were identified in excreta. For the structure of the metabolites, and the proposed metabolic pathway of diflufenzopyr, refer to Table 3.1 and Figure 3.1, respectively.

Figure 3.1 Proposed Metabolic Pathways for SAN 835 H in the Rat

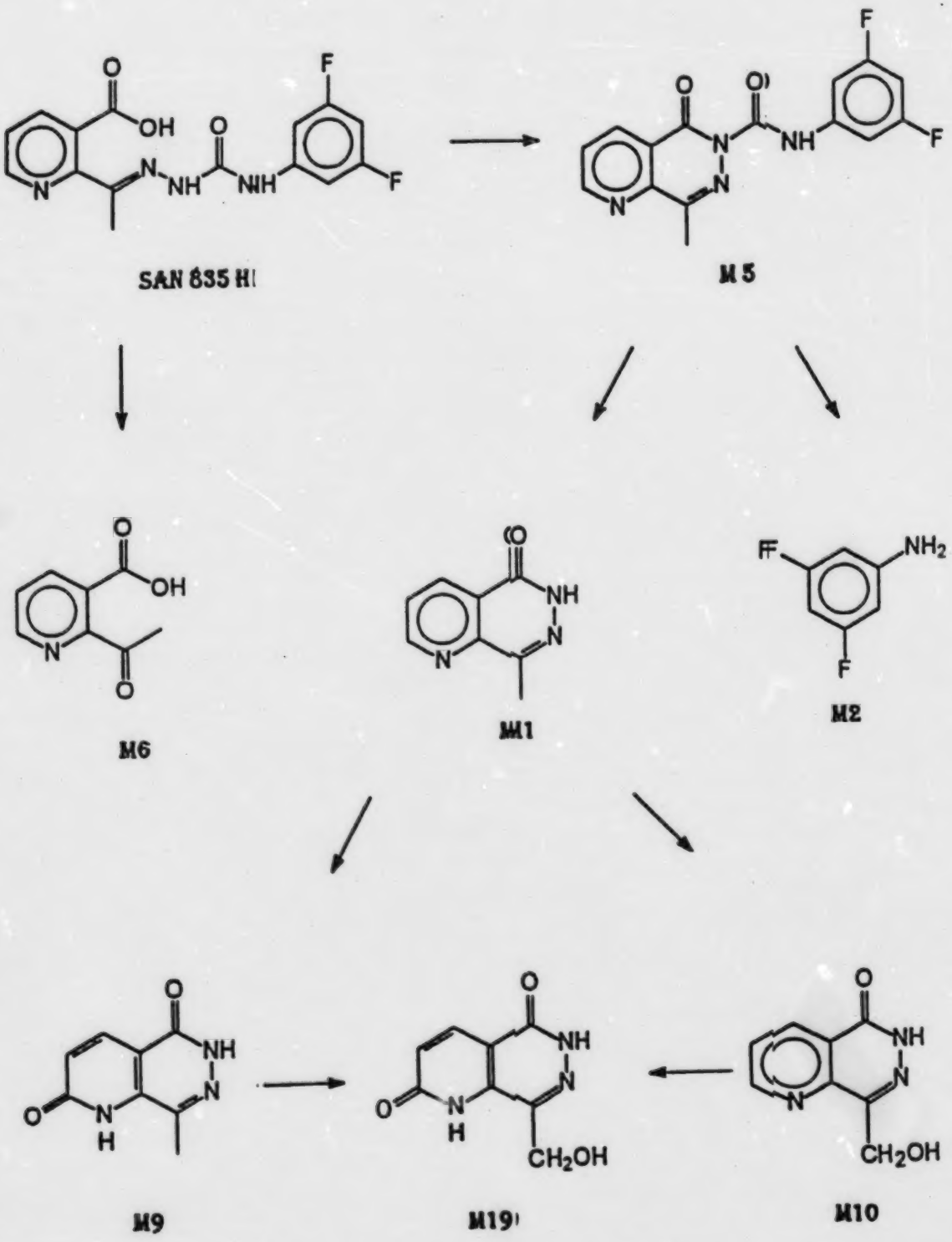


Table 3.1 TLC and HPLC Characteristics of SAN 835 H and its Model Metabolites

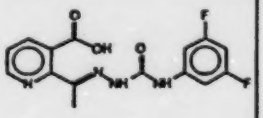
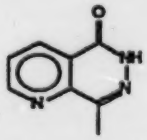
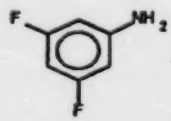
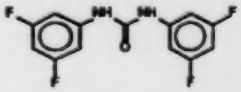
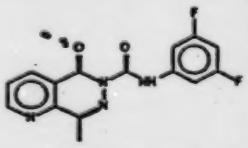
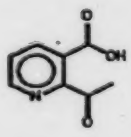
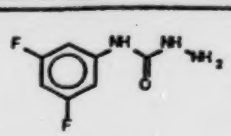
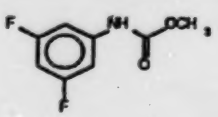
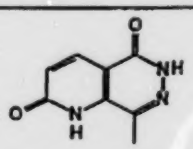
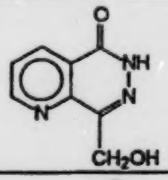
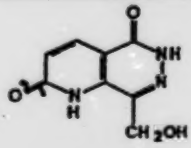
Compound designation	Structure	TLC R_f in Solvent Systems [1]						R_t (min.)
		B	L	A	I	T	N	HPLC [2]
SAN 835 H		0.45	0.43	0.31	0.55	0.57		5.2
M1 Phthalazinone		0.54	0.72	0.43	0.50	0.91		3.5
M2 3,5-difluoro-aniline		0.86	0.84	0.75				6.3
M3 Symmetric-urea		0.89	0.85	0.79				19.7
M5 Carbamoyl-Phthalazinone		0.66	0.64	0.55	0.74	0.95		8.6
M6 2-Acetyl nicotinic acid		0.37	0.16		0.42	0.54		3.5

Table 3.1 (cont'd)

Compound designation	Structure	TLC R_f in Solvent Systems [1]						R_t (min.)
		B	L	A	I	T	N	HPLC [2]
M7 Semicarbazide		0.76	0.77	0.25				4.2
M8 Carbamate		0.87	0.84	0.78				7.4
M9 2-keto-M1		0.38	0.21		0.47	0.79	0.42	3.5
M10 8-hydroxymethyl-M1		0.35	0.57	0.25		0.71		3.2
M19 2-keto-8-hydroxymethyl-M1		0.23					0.24	

[1] TLC solvent systems:

A = ethyl acetate/toluene/acetic acid/water 90:6:2:2;
B = ethyl acetate/acetic acid/water 92:4:4;
L = ethyl acetate/methanol/ammonium hydroxide 70:25:5;
I = acetonitrile/acetic acid/water 95:2.5:2.5;
T = chloroform/methanol/acetic acid/water 68:25:5:2;
N = ethyl acetate/toluene/formic acid/water 87:3:5:5.

[2] HPLC conditions:

Phenomenex Bondclone 10 C_{18} column; mobile phase isocretic acetonitrile:water (1% acetic acid) 50:50. Flow rate; 1 ml/min.

3.1.2 Acute and Dermal toxicity - technical and formulation

Diflufenzopyr, purity 96.4%, was considered to be of low acute toxicity by the oral and inhalation routes in Sprague Dawley (SD) rats (Lethal Dose 50% [LD_{50}] >5.0 g/kg bw; Lethal Concentration 50% [LC_{50}] >2.93 mg/L), and of low acute toxicity by the dermal route to New Zealand White (NZW) rabbits (LD_{50} >5.0 g/kg bw). It was non-irritating when applied to the skin of NZW rabbits, and minimally irritating when instilled into the eyes of the same species. Results of skin sensitization testing using Pirbright White Dunkin Hartley (PWDH) albino guinea pigs, employing the modified Buehler method, were negative.

Based on the results of acute toxicity testing, no signal words are required to be displayed on the primary display panel.

Distinct® herbicide, containing 20.0% diflufenzopyr and 51.0% dicamba, was considered to be slightly acutely toxic by the oral route (combined LD_{50} = 1.8 g/kg bw) and of low acute toxicity by the inhalation route (LC_{50} >5.34 mg/L) to SD rats, and of low acute dermal toxicity (LD_{50} >5.0 g/kg bw) to NZW rabbits. It was slightly irritating when applied to the skin of NZW rabbits, and moderately irritating when instilled into the eyes of the same species. Results of skin sensitization testing using PWDH albino guinea pigs, employing the modified Buehler method, were positive.

Based on the results of acute toxicity testing, it is recommended that the words "CAUTION POISON", "CAUTION EYE IRRITANT" and "POTENTIAL SKIN SENSITIZER" be displayed on the primary panel of the label.

Technical diflufenzopyr, purity 96.4%, was moistened with distilled water and administered by dermal application to male and female NZW rabbits at dose levels of 0, 100, 300 and 1000 mg/kg bw per application, five rabbits per sex per group. Frequency of application was six hours per day, daily, for 21–24 consecutive days.

The no observed effect level (NOEL) for systemic toxicity was determined to be 1000 mg/kg bw/d, since there were no apparent signs of treatment-related systemic effects observed in male or female rabbits at any dose level tested.

A NOEL for dermal effects could not be determined since local dermal irritation was observed at all dose levels tested (there were no corresponding findings upon histopathological examination).

Distinct® herbicide, containing 20.0% diflufenzopyr and 51.0% dicamba, was moistened with distilled water and administered by dermal application to male and female NZW rabbits at dose levels of 0, 10, 30 and 100 mg/kg bw per application, five rabbits per sex per group. Frequency of application was six hours per day, daily, for 21–24 consecutive days.

The NOEL for systemic toxicity was determined to be 100 mg/kg bw/d, since there were no apparent signs of treatment-related systemic effects observed in male or female rabbits at any dose level tested.

A NOEL for dermal effects could not be determined since local dermal irritation was observed at all dose levels tested. Corresponding findings upon histopathological examination were noted in the 30- and 100-mg/kg bw/d groups only, and included diffuse acanthosis and diffuse/focal inflammation of the superficial dermis. In addition, diffuse hyperkeratosis was observed in the 100-mg/kg bw/d group only.

3.1.3 Genotoxicity

In a microbial reverse gene mutation study (in vitro) using the standard plate incorporation assay, *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 were exposed to diflufenzopyr, purity 98.9%, vehicle dimethylsulfoxide (DMSO). Dose levels chosen were 0 (vehicle control), 667, 1000, 6667 and 10,000 µg/plate, both in the presence and absence of metabolic activator (i.e., S9 fraction derived from Aroclor 1254-induced SD male rat livers). No appreciable cytotoxicity was seen at any of these dose levels. All strains responded in the expected manner to the appropriate positive control. There was, however, no evidence that diflufenzopyr induced a mutagenic effect in any strain at any dose level tested.

Hence, under the conditions of this study, diflufenzopyr was considered non-mutagenic for point mutation.

In a repeat, gene mutation study (in vitro) using the standard plate incorporation assay, *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 were exposed to diflufenzopyr, purity 97.1%, vehicle DMSO. Dose levels chosen were 0 (vehicle control), 333, 667, 1000, 3330, 6670 and 10,000 µg/plate, both in the presence and absence of metabolic activator (i.e., S9 fraction derived from Aroclor 1254-induced SD male rat livers). No cytotoxicity was observed at any of these dose levels. All strains responded in the expected manner to the positive controls. However, there was no evidence that diflufenzopyr induced a mutagenic response at any dose level tested.

Hence, under the conditions of this study, diflufenzopyr was considered non-mutagenic for point mutation.

In an in vitro forward mutation assay with independent repeat, cultured L5178Y (TK+/−) mouse lymphoma cells were exposed for four hours to diflufenzopyr, purity 97.1%, dissolved in DMSO, at eight dose levels ranging from 0.05 to 3.0 mg/mL, both in the presence and absence of metabolic activator. The confirmatory trial investigated nine doses ranging from 0.05 to 2.0 mg/mL, both in the presence and absence of metabolic activator. The metabolic activator was S9 homogenate from Aroclor 1254-induced SD male rat liver.

Diflufenzopyr was insoluble at ≥2500 µg/mL. Cytotoxicity was seen at ≥2.0 mg/mL and ≥1.8 mg/mL, in the absence and presence of metabolic activator, respectively. Lower

concentrations resulted in an adequate range of relative total growth values to allow for an adequate assessment of mutagenic potential (i.e., 10–95% of the control values). The positive controls induced the expected mutagenic responses. There was, however, no evidence that diflufenzopyr was mutagenic at any dose under any assay condition.

Under the conditions of this assay, diflufenzopyr was considered non-mutagenic.

An in vitro unscheduled deoxyribonucleic acid (DNA) synthesis assay was conducted on rat hepatocytes prepared from an adult male Fischer 344 rat, using technical diflufenzopyr, purity 97.1%. Dose levels chosen were 0 (solvent control), 5, 10, 25, 50, 100 and 250 µg/mL, both in the presence and absence of metabolic activator. The metabolic activator was S9 homogenate derived from Aroclor 1254-induced rat livers and the test material was delivered to the test system as a solution in DMSO.

Under the conditions of this assay, it was concluded that diflufenzopyr did not induce unscheduled DNA synthesis.

In an in vivo mammalian cytogenetics (micronucleus) assay, groups of ICR mice (five per sex per dose per sacrifice time) were gavaged orally with single doses (12.5 mL/kg bw) of corn oil (vehicle control), or diflufenzopyr, purity 97.1% (500, 1667 and 5000 mg/kg bw), or positive control material (cyclophosphamide, 80 mg/kg bw). Twenty-four, 48 and 72 h after dosing, five mice per sex per group in the diflufenzopyr-treated groups were sacrificed; all mice in the vehicle and positive control groups were sacrificed 24 h post-dosing. Slides were prepared from harvested bone marrow, and were evaluated for the presence of micronucleated polychromatic erythrocytes (MPCEs) as well as possible cytotoxicity (ratio of polychromatic erythrocytes [PCEs] to total erythrocytes). No mortalities occurred during the micronucleus assay. The positive control induced the expected high yield of MPCEs in mice sacrificed at 24 h. Diflufenzopyr did not induce a clastogenic effect in either sex at any sacrifice time.

Under the conditions of this assay, it was concluded that diflufenzopyr was non-clastogenic.

3.1.4 Sub-chronic and chronic toxicity

The sub-chronic and chronic toxicity of diflufenzopyr were investigated in mice, rats and dogs. Ninety-day studies were conducted, which were used to establish appropriate dose levels to be used in the long-term studies.

3.1.4.1 Sub-chronic and chronic toxicity in the mouse

Male and female CD-1 mice were fed test diets containing technical diflufenzopyr, purity 97.1%, at dietary concentrations of 0, 350, 1750, 3500 and 7000 ppm (equal to 0, 58, 287, 613 and 1225 mg/kg bw/d for males, and 0, 84, 369, 787 and 1605 mg/kg bw/d for females) for a period of 13 weeks (wk), 10 mice per sex per group. The NOEL was determined to be 7000 ppm (equal to 1225 mg/kg bw/d for males and

1605 mg/kg bw/d for females) since there were no treatment-related effects observed in male or female mice at any dose level tested.

Based on the results of this study, the dose levels chosen for the mouse chronic oncogenicity feeding study were 0, 700, 3500 and 7000 ppm (limit dose).

Male and female CD-1 mice were fed test diets containing technical diflufenzopyr, purity 98.1%, at dietary concentrations of 0, 700, 3500 and 7000 ppm (equal to 0, 100, 517 and 1037 mg/kg bw/d for males, and 0, 98, 500 and 1004 mg/kg bw/d for females), 60 mice per sex per group, for a period of 78 wk. An interim sacrifice was carried out after 52 wk on treatment, 10 pre-selected mice per sex per group.

The NOEL for systemic toxicity for males was determined to be 7000 ppm (equal to 1037 mg/kg bw/d) since there were no treatment-related effects observed at any dose level tested. For females, the no observed adverse effect level (NOAEL) was determined to be 7000 ppm (1004 mg/kg bw/d). This was based on a slight, but statistically significant lower mean overall body weight gain for females in the 7000-ppm group, due primarily to decreased gain/increased weight loss during the second year of the study. In the absence of any other treatment-related findings, this was not considered to be an adverse, toxicologically significant finding.

There was no evidence of oncogenic potential of diflufenzopyr for male or female mice at any dose level tested.

3.1.4.2 Sub-chronic and chronic toxicity in the rat

Male and female Wistar rats were fed test diets containing technical diflufenzopyr, purity 96%, at dose levels of 0, 1000, 5000, 10,000 and 20,000 ppm (equal to 0, 60.8, 352, 725 and 1513 mg/kg bw/d for males, and 0, 72.8, 431, 890 and 1750 mg/kg bw/d for females) for a period of 13 wk, 10 rats per sex per group. An additional 10 rats per sex were assigned to the 0- and 20,000-ppm groups for a four-week recovery period following treatment.

The NOEL was set at 5000 ppm (equal to 352 mg/kg bw/d for males, and 431 mg/kg bw/d for females) based on lower mean body weight gain and decreased food efficiency in the 10,000- and 20,000-ppm groups, both sexes. Additional findings were decreased food intake (20,000 ppm, males only); slight increases in cholesterol (20,000 ppm, both sexes, and 10,000 ppm, males only) and alanine aminotransferase (10,000 and 20,000 ppm, both sexes); and slightly lower chloride (20,000 ppm, both sexes). Histopathological findings were an increased incidence of foamy macrophages in the lungs in the 10,000- and 20,000-ppm group, both sexes, and testicular atrophy in the 20,000-ppm group.

Following the four-week recovery period, the only treatment-related effects that showed partial or no evidence of recovery were foamy macrophages in the lungs and testicular atrophy.

Male and female Wistar rats were fed test diets containing technical diflufenzopyr, purity 97.1–99.6%, at dietary concentrations of 0, 500, 1500, 5,000 and 10,000 ppm (equal to 0, 22, 69, 236 and 518 mg/kg bw/d for males, and 0, 29, 93, 323 and 697 mg/kg bw/d for females), 72 rats per sex per group, for a period of 104 wk. An interim sacrifice was carried out after 52 wk on treatment, 20 pre-selected rats per sex per group. The NOAEL for systemic toxicity was set at 5000 ppm (equal to 236 mg/kg bw/d for males and 323 mg/kg bw/d for females) based on slightly lower final body weights in the 1500- and 5000-ppm groups. However, this was due to decreased body weight gain seen primarily in the second year of the study, and only attained a 10% reduction (compared to the concurrent control value), between study weeks 91 and 106. In addition, there were no other treatment-related effects noted in the 1500- and 5000-ppm groups; hence, these body weight changes were not considered to be toxicologically significant. Treatment-related effects in the 10,000-ppm group were significantly lower body weight and body weight gains throughout the study period, and decreased food efficiency.

There was no evidence of oncogenic potential of diflufenzopyr at any dose level tested.

3.1.4.3 Sub-chronic toxicity in the dog

Male and female beagle dogs were fed test diets containing technical diflufenzopyr, purity 98%, at dietary concentrations of 0, 1500, 10,000 and 30,000 ppm (equal to 0, 58, 403 and 1121 mg/kg bw/d for males, and 0, 59, 424 and 1172 mg/kg bw/d for females) for a period of 90 d, four dogs per sex per group.

The NOEL was 1500 ppm (equal to 58 mg/kg bw/d) based on erythroid hyperplasia in the bone marrow and extramedullary hematopoeisis in the liver, evident in the 10,000- and 30,000-ppm groups. The only other finding in the 10,000-ppm group, which was considered to possibly be related to treatment, was hemosiderin deposits noted in the Kupffer cells of one female dog. Additional treatment-related findings noted in the 30,000-ppm group were absence of fatty bone marrow, dry skin/non-specific skin lesions, lower body weight gain and food consumption, regenerative anemia (i.e., reticulocytosis, anisocytosis, polychromasia, normoblasts, higher mean corpuscular volume [MCV], lower mean corpuscular hemaglobin concentration [MCHC]), hemosiderin deposits in Kupffer cells and macrophages, extramedullary hematopoeisis in the lungs, lymph nodes and kidneys, depressed myeloid/erythroid ratio in the bone marrow, higher spleen, liver and kidney weights (females only), and urothelial hyperplasia and cystitis.

Male and female beagle dogs were fed test diets containing technical diflufenzopyr, purity 98%, at dietary concentrations of 0, 750, 7500 and 15,000 ppm (equal to 0, 26, 299 and 529 mg/kg bw/d for males and 0, 28, 301 and 538 mg/kg bw/d for females) for a period of 52 wk, four dogs per sex per group.

The NOEL was determined to be 750 ppm (equal to 26 mg/kg bw/d) based on erythroid hyperplasia in the femoral and sternal bone marrow, accompanied by an increase in hemosiderin deposits in the kidneys, liver and spleen, and reddish discolouration of the

diaphysis of the femur; mild to moderate reticulocytosis; and slightly lower body weight gain and less efficient food utilization (females only) in the 7500- and 15,000-ppm groups. The only other findings considered to be treatment-related were higher MCV and lower MCHC in the 15,000-ppm group.

3.1.5 Reproductive and developmental toxicity

A two-generation reproduction study was conducted using SD rats, fed test diets containing diflufenzopyr, purity 98.1%, at concentrations of 0, 500, 2000 and 8000 ppm (equal to 0, 27.3, 113.1 and 466.2 mg/kg bw/d for males, and 0, 42.2, 175.9 and 742.0 mg/kg bw/d for females), 26 per sex per group, continuously throughout the study period. Each female in the P generation was mated to produce two litters, whereas the F_1 generation (i.e., from the F_1a litters) was mated to produce one litter only.

In the 8000-ppm group, mean body weight gains were lower for males and females during pre-mating (P and F generation) and for females during gestation (F_1a, F_1b and F_2a litters), and mean food consumption was increased for P and F generation males during pre-mating, for F generation females during pre-mating and for females during gestation with the F_1a, F_1b and F_2a litters. In the 2000-ppm group, slightly lower mean body weight gain for P generation males during the pre-mating period, and marginally increased mean food consumption for P generation males and for F_1 generation females during pre-mating only were considered to be treatment-related, but were not considered adverse. The only other parental treatment-related finding was slightly increased mean seminal vesicle weight in the 2000-and 8000-ppm groups. In the absence of any corresponding gross or histopathological findings, however, this was not considered to be an adverse effect.

The F_2 generation pups dosed at 8000 ppm had lower live birth and viability indices and the total pre-perinatal loss was significantly increased. Mean body weight was decreased in the 8000-ppm group in the F_1a generation for both sexes on day 21 of lactation, due to lower mean body weight gains on days 4–21 of lactation. In the 8000-ppm group, F_1a and F_1b generations had a higher proportion of runts and the F_2 generation had a higher percentage of offspring with no milk in the stomach.

Based on the results obtained from this study, the NOAEL for parental toxicity was determined to be 2000 ppm, and the NOEL for reproductive toxicity was set at 2000 ppm (equal to 113.1 mg/kg bw/d for males, and 175.9 mg/kg bw/d for females).

Pregnant SD rats (Crl:CD BR) were dosed by gavage with technical diflufenzopyr, purity 98.1%, as a suspension in aqueous 0.5% methylcellulose, at dose levels of 0 (vehicle control), 100, 300 and 1000 mg/kg bw/d, 25 mated females per group, from day 6 to 15 of gestation, inclusive.

The NOAEL for maternal toxicity was set at 1000 mg/kg bw/d based on slightly reduced mean maternal body weight gain and mean food consumption during the first three days of dosing, evident in the 1000-mg/kg bw/d treatment group only. This finding did not attain statistical significance and mean final body weights were comparable among all

groups. Hence, this was not considered to be an adverse, toxicologically significant effect. There were no other maternal, treatment-related effects.

The NOAEL for developmental toxicity was set at 1000 mg/kg bw/d based on an increased incidence of incompletely ossified and/or unossified sternal centra at that dose level. In the absence of any other treatment-related findings or induced malformations, this minor variation was not considered to be an adverse, toxicologically significant finding.

There was no evidence of any teratogenic effects related to treatment with diflufenzopyr at any dose level tested.

Pregnant NZW rabbits were dosed by gavage with technical diflufenzopyr, purity 98.1%, as a suspension in aqueous 0.5% methylcellulose, at dose levels of 0, 30, 100 and 300 mg/kg bw/d, 20 pregnant females per group, from day 6 to 19 of gestation, inclusive.

The NOEL for maternal toxicity was set at 100 mg/kg bw/d based on an increased incidence of mortality, abnormal feces and abortions, and a slight but persistent mean weight loss and lower mean food consumption during the dosing period, evident in the 300-mg/kg bw/d treatment group.

The NOEL for developmental toxicity was set at 100 mg/kg bw/d based on an increased incidence of abortions in the 300-mg/kg bw/d group (a maternally toxic dose). There were no other treatment-related fetotoxic effects.

There was no evidence of any teratogenic effects related to treatment with diflufenzopyr at any dose level tested.

3.1.6 Neurotoxicity (acute, delayed and sub-chronic)

Male and female Crl:CD BR rats were dosed once by oral gavage with diflufenzopyr, purity 96.4%, as a suspension in 1% methylcellulose, at dose levels of 0, 125, 500 and 2000 mg/kg bw, 10 rats per sex per group. Special neurological examinations included a Functional Observational Battery (FOB) and motor activity testing (in-life), and a detailed histopathological examination of perfused central and peripheral nervous system tissues.

The NOEL was determined to be 2000 mg/kg bw since there were no treatment-related effects observed in male or female rats at any dose level tested.

Data on delayed neurotoxicity have not been generated, and are not considered relevant for compounds such as diflufenzopyr.

Male and female Crl:CD BR rats were fed test diets containing technical diflufenzopyr, purity 96.4%, at levels of 0, 25, 75 and 1000 mg/kg bw/d, 10 rats per sex per group, for a period of 13 wk. Special neurological examinations included an FOB and motor activity

testing (in-life), and a detailed histopathological examination of perfused central and peripheral nervous system tissues.

The NOEL was determined to be 75 mg/kg bw/d based on lower body weight gain and lower feed efficiency in the 1000-mg/kg bw/d group. There were no other treatment-related effects observed at any dose level tested.

There was no indication of neurotoxicity observed at any dose level tested.

3.1.7 **Overall toxicological summary** (refer to Appendix I)

A detailed review of the toxicity data base available for the new herbicide diflufenzopyr has been completed. Data submitted were complete and well presented, and included the full battery of studies required for registration purposes. Studies were well conducted and in conformance with acceptable international testing protocols.

Results from metabolism studies demonstrated that after oral administration, a smaller percentage of the administered dose (AD) was excreted in the urine and more in the feces, when compared to intravenous administration, indicating that diflufenzopyr was only partially absorbed following oral dosing. Within 72 h after oral dosing, the majority of the AD was eliminated via the feces (i.e., 49–79%) whereas only 20–44% of the AD was excreted in the urine. After intravenous dosing, 61–89% of the AD was excreted in the urine. Sex, dose level and pre-treatment had little effect on the excretion pattern. Three- to 19% of the AD was recovered in the bile of all dose groups, indicating that enterohepatic circulation played a role in the elimination of diflufenzopyr. The approximate half-life of diflufenzopyr was 5.3–6.9 h for all single oral and intravenous dose groups, and 7.7–10.8 h for the repeat oral dose group.

Diflufenzopyr did not accumulate in the tissues; TRRs accounted for <3% of the AD for all dose groups. Residue levels were highest in blood, red blood cells and serum for the phenyl-labelled groups, and were highest in liver and kidney for the pyridinyl-labelled groups.

The major fraction of TRR extracted from urine, feces and bile was identified as unchanged diflufenzopyr. In addition, minor amounts of hydrolysis products M1, M5 and M6, and hydroxylation products M9, M10 and M19 were identified in excreta.

Acute single dosing revealed that technical diflufenzopyr was of low toxicity to laboratory animals by the oral, inhalation and dermal routes, whereas the Distinct® formulation was slightly toxic by the oral route, and of low toxicity by the dermal and inhalation routes. The technical material was non-irritating to rabbit skin and did not possess potential skin sensitizing properties when tested on guinea pigs (modified Buehler method), whereas Distinct® was slightly irritating to the skin of rabbits and was a potential skin sensitizer. The technical material was minimally irritating to the rabbit eye, whereas the formulation induced moderate eye irritation.

Short-term repeated dermal (21–24 d) dosing in rabbits with technical diflufenzopyr or the Distinct® formulation did not result in any treatment-related systemic effects up to and including the highest dose levels tested of 1000 mg/kg bw/d and 100 mg/kg bw/d, respectively. However, local dermal irritation was observed at all dose levels tested for both diflufenzopyr (low dose of 100 mg/kg bw/d) and Distinct® (low dose of 10 mg/kg bw/d).

In mice, short-term (13 wk) and long-term (78 wk), dietary exposure to technical diflufenzopyr did not result in any toxicologically significant treatment-related effects up to and including the highest dose level tested of 7000 ppm (equal to 1225 mg/kg bw/d for males and 1605 mg/kg bw/d for females in the 13-wk study; and equal to 1037 mg/kg bw/d for males and 1004 mg/kg bw/d for females in the 78-wk study).

Technical diflufenzopyr administered orally to dogs for either 13 weeks or one year resulted in erythroid hyperplasia in the bone marrow, extramedullary hematopoiesis in the liver, hemosiderin deposits in various organs and mild to moderate reticulocytosis. (These effects were not observed in any other species tested.) These findings indicate that the test material was directly toxic to dog erythrocytes, with a compensatory response in the bone marrow and liver (i.e., a responsive hemolytic anemia). The NOEL for these findings was 1500 ppm (58 mg/kg bw/d) after 13 wk of treatment, and 750 ppm (26 mg/kg bw/d) after 52 wk of treatment. Lower body weight gain was evident at dose levels ≥15,000 ppm.

In rats, body weight gain was lower after short-term (13 wk) and long-term (104 wk) exposure at dose levels ≥10,000 ppm (equal to 518 mg/kg bw/d for males and 697 mg/kg bw/d for females). Slightly lower body weight gain was also observed for females in the 5000 ppm group (equal to 323 mg/kg bw/d) after one year on treatment, but only attained a 10% reduction compared to the concurrent control group and was not considered to be toxicologically significant. After short-term exposure, an increased incidence of foamy macrophages in the lungs was noted in the 10,000- and 20,000-ppm groups, both sexes, and an increased incidence of testicular atrophy was seen in the 20,000-ppm group. However, these findings were not observed after long-term exposure at dose levels up to and including 10,000 ppm.

Life-time studies did not demonstrate any evidence of oncogenic/carcinogenic potential of diflufenzopyr in rats and mice. In addition, all in vitro and in vivo mutagenicity assays conducted yielded negative results for genotoxic potential.

Diflufenzopyr affected reproductive performance in rats at the high dose of 8000 ppm (equal to 466.2 mg/kg/bw-d), manifested as lower live birth and viability indices, increased pre-perinatal loss and an increased number of runts. In addition, mean body weights for offspring in the F_1a generation were lower on day 21 postpartum due to lower body weight gain on days 4–21 of lactation. The only parental finding was decreased mean body weight and body weight gain, evident in parents in the 8000-ppm group during premating (P and F generation); and in 8000 ppm females during gestation (all litters). Hence, the systemic NOEL was set at the next lower dose of 2000 ppm (equal to 113.1 mg/kg bw/d). A slight increase in mean seminal vesicle weight was

noted for parental males in the 2000- and 8000-ppm groups, but was not considered adverse since there were no corresponding gross or histopathological findings.

Diflufenzopyr was not teratogenic to rat or rabbit fetuses at dose levels up to and including 1000 mg/kg bw/d (rats) and 300 mg/kg bw/d (rabbits). Fetotoxicity was noted in rabbit fetuses at 300 mg/kg bw/d (a maternally toxic dose), manifested as an increased incidence of abortions. The only treatment-related finding for rat fetuses was an increased incidence of incompletely ossified and/or unossified sternal centra noted for rat fetuses in the 1000-mg/kg bw/d group. However, this minor variation was not considered to be an adverse, toxicologically significant finding. Maternal findings were observed in rabbits at 300 mg/kg bw/d only and included loss of body weight and decreased food intake during the dosing period, and increased mortality. The only maternal effect seen in rats was slightly lower (non-adverse) body weight gain and lower food intake noted during the first three days of dosing in the 1000 mg/kg bw/d group.

Diflufenzopyr showed no evidence of neurotoxicity in rats by either acute or subchronic exposure up to and including the highest dose levels tested of 2000 and 1000 mg/kg bw/d, respectively.

Table 3.2 Summary of the sub-chronic and chronic toxicity studies with diflufenzopyr

Type of study	Species	NOEL/NOAEL (mg/kg bw/d)
Oral route, 90 d	mice	1225 in males, 1605 in females
Oral route, 90 d	rats	352 in males, 431 in females
Oral route, 90 d	dogs	58 in males, 59 in females
Dermal route, 28 d	rabbit	1000 for both sexes
Genotoxicity (in vitro and in vivo)	---	negative
Oral route, 1 yr	dogs	26 for males, 28 for females
Oral route, 78 wk	mice	1037 for males, 1004 for females
Oral route, 104 wk	rats	236 for males, 323 for females
Carcinogenicity	mice	1037 for males, 1004 for females
Carcinogenicity	rats	518 for males, 697 for females
Multigeneration	rats	Systemic and Reproductive: 113.1 for males, 175.9 for females
Teratogenicity	rats	Maternal, fetotoxic and teratogenic: 1000
Teratogenicity	rabbits	Maternal, fetotoxic: 100 Teratogenic: 300
Acute oral neurotoxicity	rats	Systemic, neurotoxic: 2000, both sexes Systemic: 75, both sexes
Neurotoxicity, 13 wk	rats	Neurotoxic: 1000, both sexes

3.2 Determination of acceptable daily intake

The lowest NOEL was 750 ppm, equal to 26 mg/kg bw/d, established in the one-year dog feeding study, based on treatment-related hemolytic anemia (responsive) at higher dose levels. This is considered an appropriate study for determination of the acceptable

daily intake (ADI), since the dog was the most sensitive species, and there was no evidence of treatment-related oncogenicity in rats or mice, nor reproductive/developmental effects in rats and rabbits.

For the calculation of the ADI, a safety factor (SF) of 100 is proposed.

The ADI proposed is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOEL}}{\text{SF}} = \frac{26 \text{ mg/kg bw/d}}{100} = 0.26 \text{ mg/kg bw/d of diflufenzopyr}$$

The maximum acceptable intake for a 60-kg person, calculated according to the formula, ADI × 60 kg, is 15.6 mg/d.

3.3 Acute reference dose

If an acute reference dose (ARfD) is required, the study considered most appropriate in the submitted toxicological data base is the rabbit teratology study. The dose and endpoint selected for risk assessment is 100 mg/kg bw/d based on an increased incidence of abortions noted at 300 mg/kg bw/d, the highest dose level tested. Abortions are considered an appropriate endpoint since they could result from either maternal and/or developmental toxicity after short-term (i.e., 14 d) exposure by oral gavage.

For the calculation of the ARfD, a SF of 100 is proposed.

The ARfD proposed is calculated according to the following formula:

$$\text{ARfD} = \frac{100 \text{ mg/kg bw/d}}{100} = 1.0 \text{ mg/kg bw/d of diflufenzopyr}$$

3.4 Toxicology endpoint selection for occupational and bystander risk assessment

The formulation is slightly acutely toxic by the oral route, and of low acute toxicity by the dermal and inhalation routes. It is a slight skin irritant and a moderate eye irritant. Results of skin sensitization studies were positive.

Given the short-term nature of the exposure for farmers (one to several days per year), and the predominantly dermal exposure route, a dermal toxicity study is considered to be the most relevant to use in the risk assessment. A 21-d dermal rabbit study with diflufenzopyr technical was well conducted and did not demonstrate any systemic toxic effects at 1000 mg/kg bw/d, the highest dose tested. A NOEL for dermal effects could not be determined since local dermal irritation was observed at all doses tested, although there were no corresponding histopathological findings. A 21-d dermal rabbit study was also conducted with the Distinct® formulation (20% diflufenzopyr; 50% dicamba). This study was well conducted and did not demonstrate any systemic toxic effects at 100 mg formulation/kg bw/d, the highest dose tested. Local dermal irritation was observed at all doses tested, with corresponding histopathological findings in the 30- and

100-mg formulation/kg bw/d dose groups. These effects included diffuse acanthosis and diffuse/focal inflammation of the superficial dermis. In addition, diffuse hyperkeratosis was observed in the 100-mg/kg bw/d group. The systemic NOEL of 1000 mg/kg bw/d determined with the diflufenzopyr technical is considered most relevant for risk assessment.

The 21-d dermal study is not considered relevant for the longer-term custom applicators, due to their longer exposure period (several weeks per year). Based on the NOELs determined in short- and long-term studies, dogs were the most sensitive species tested. The NOEL of 58 mg/kg bw/d, determined in a three-month dog feeding study, was considered the most relevant to use in the risk assessment for custom applicators. This NOEL was based on erythroid hyperplasia in the bone marrow and extramedullary hematopoeisis in the liver at higher dose levels (i.e., 403 and 1121 mg/kg bw/d). Regenerative anaemia was evident at 1121 mg/kg bw/d only. Similar findings were seen in the one-year dog feeding study, at dose levels ≥299 mg/kg bw/d.

In a two-generation rat reproductive study, the NOAEL for parental toxicity and the NOEL for reproductive toxicity were the same: 113 and 176 mg/kg bw/d for males and females respectively. There was no evidence of teratogenic effects in rats or rabbits at any dose level tested.

Mutagenicity testing showed negative findings. There were no signs of oncogenic potential or neurotoxicity.

3.5 Drinking water limit

See Section 4.2.

3.6 Impact on human and animal health arising from exposure to the active substance or to impurities contained in it

3.6.1 Operator exposure and risk assessment

A farmer applying Distinct® by ground equipment would typically treat 90 ha/d and be exposed for one or two days per season. A custom applicator could treat up to 400 ha/d and be exposed intermittently for several weeks per growing season.

Pesticide operator exposure was estimated using the Pesticide Handler Exposure Database (PHED) Version 1.1. The PHED is a compilation of generic mixer/loader/ applicator and flagger passive dosimetry data with associated software that facilitates the generation of scenario specific exposure estimates. The following PHED estimates meet North American Free Trade Agreement (NAFTA) criteria for data quality, specificity and quantity.

To estimate total dermal and inhalation exposure for groundboom application, appropriate subsets of A and B grade data were created from the mixer/loader and from the applicator PHED database files. There were no relevant data available in the

mixer/loader/applicator database file. The mixer/loader file was subset for open mixing, dry flowable formulations and to exclude replicates for packaging in water soluble packets. The applicator file was subset for application by groundboom tractor or truck with open cabs. The number of replicates for inhalation and dermal data were acceptable (range 16–40). In the PHED subsets, the mean and range of pesticide mixed and applied and the sampling time were of the same order of magnitude as the estimated 5.1 kg a.i./d handled by a farmer treating 90 ha with 57 g a.i./ha in an eight-hour workday.

Protective clothing specified on the label for mixer/loaders are long-sleeved shirts, long pants, shoes and socks, chemical-resistant gloves and protective eyewear (face shield or safety glasses). Exposure was estimated for mixer/loaders wearing long pants, long-sleeved shirts and gloves and for applicators wearing long pants, long-sleeved shirts and no gloves. The PHED Version 1.1 uses actual data and does not assume clothing penetration factors.

All data were normalized for kg/a.i. handled. Exposure estimates are presented on the basis of the "best-fit" measure of central tendency (i.e., on summing the measure of central tendency for each body part that is most appropriate to the distribution of data for that body part [arithmetic mean if normal distribution, geometric mean if lognormal distribution, median if any other distribution]). Exposure estimates and margin of exposure calculations were based on (1) farmers mixing/loading and applying Distinct® at 57 g a.i./ha to 90 ha/d on a few days per growing season and (2) custom applicators mixing/loading and applying Distinct® at 57 g a.i./ha to 400 ha/d intermittently over several weeks. Exposure was predominantly dermal. As no percutaneous absorption data were available, the default assumption was 100% absorption[1].

Although the PHED does not include data from which to estimate exposure during clean-up/repair activities, PHED data provide an adequate basis for estimating occupational exposure for the proposed use.

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1 The EPA estimated dermal absorption at 3%, based on comparing a maternal NOAEL of 30 mg/kg bw/d established in an oral developmental study in rabbits and the NOAEL of 1000 mg/kg bw/d established in the 21-d dermal absorption study in the same species. This approach has not yet been tabled for discussion by the NAFTA Harmonization Working Group on dermal absorption.

Table 3.3 Estimated operator exposure and resulting margins of exposure[2]

Operator exposure scenario		Daily exposure (dermal + inhalation) 70-kg operator (mg/kg bw/d)	Margin of exposure (NOEL/exposure)
Application at 57 g a.i./ha. Mixer/loaders wearing long pants, long-sleeved shirts and gloves. Applicators wearing long pants, long-sleeved shirts and no gloves.	Farmer: Mixer/loader/applicator treating 90 ha	0.015	67,000[a]
	Custom applicator: Mixer/loader treating 400 ha	0.054	1100[b]
	Custom applicator: Applicator treating 400 ha	0.011	5300[b]
	Custom applicator: Mixer/loader/applicator treating 400 ha	0.065	900[b]

[a] Based on a NOEL of 1000 mg/kg bw/d from a 21-d dermal rabbit study.
[b] Based on a NOEL of 58 mg/kg bw/d from a three-month dog feeding study and a default assumption of 100% dermal absorption.

The margins of exposure, calculated on the basis of typical Canadian use patterns, are acceptable for both farmers and custom applicators.

3.6.2 Bystanders

Given that application is by ground equipment only, and the proposed agricultural use scenario, exposure and risk should be minimal.

3.6.3 Workers

Data are not available to make a quantitative estimate of re-entry exposure. However, the proposed use pattern is such that re-entry exposure should be minimal. Application is at a pre- or post-emergence stage (up to 60 cm crop height). Workers may re-enter treated

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[2] Based on the NOEL of 1000 mg/kg bw/d in the 21-d dermal rabbit study, estimated dermal penetration of 3% and the lowest relevant oral NOEL, the EPA considered the dermal equivalent NOEL to exceed a limit dose of 1000 mg/kg bw/d and, therefore, did not require a short- or intermediate-term dermal occupational risk assessment. The EPA selected the NOEL of 58 mg/kg bw/d from the three-month dog feeding study as the appropriate endpoint for inhalation exposure. Based on this, and inhalation exposure estimates from the PHED Version 1.1, the EPA calculated margins of exposure in excess of 40,000 for custom applicators and in excess of 95,000 for farmers. The PMRA used the same oral endpoint (58 mg/kg bw/d) to calculate margins of exposure for combined inhalation and dermal exposure.

fields to monitor crops to assess efficacy, typically 7–10 d following application, but these tasks would involve little foliar contact and, thus, minimal exposure and risk.

Based on the acute toxicity profile, the restricted entry interval should be 12 h.

4.0 Residue

4.1 Definition of the residues relevant to maximum residue limits

4.1.1 Definition of the residues in corn relevant to maximum residue limits

Corn Metabolism Study
Corn metabolism studies were performed under field conditions in microplots without soil containment. These showed that when corn was treated at four times the proposed rate and near the proposed 4- to 6-leaf stage, TRRs in corn silage, fodder, forage and grain were 0.15, 0.17, 0.4 and 0.008 ppm, respectively. No parent compound was detected. Major metabolites (≥10% TRR and/or ≥0.05 ppm) identified were, in decreasing order, M1, M10 (free and as its glucoside) and M9. Minor metabolites, M19 and glucoside of M19 (M29), were also identified.

Total radioactive residues (both ^{14}C-pyridine and ^{14}C-phenyl labels) in grain were <0.01 ppm at 4× the proposed rate. It is, therefore, expected that when diflufenzopyr is used according to the proposed rate, the TRRs in corn grain will be even lower.

Diflufenzopyr was not detected in the metabolism studies due to its rapid degradation to M1. Therefore, the ROC may be defined as the parent compound and its metabolites convertible to M1.

Confined Crop Rotation Study
Field plots for corn metabolism study were used for the submitted crop rotational study. Leafy vegetable (lettuce), root vegetable (carrots), and small grain cereal (barley) crops were planted in the corn metabolism plots at 30, 120 and 365 d after treatment of the corn.

The EPA concluded that this study did not fully conform to prescribed protocols. However, the EPA determined that a four-month plantback restriction based on the U.S. dicamba label was adequate for diflufenzopyr formulation. The PMRA will not require a plantback restriction since the Canadian dicamba labels do not require one.

The PMRA concluded that the protocol employed was adequate to support the absence of a label plantback restriction. The crop rotational study indicated that the application rate was 224 g a.i./ha (4× the Canadian label rate) and the test solution was sprayed to two rows of corn seedlings with 80% of the test solution estimated to reach the soil. The environmental chemistry/fate review indicated that the half-life for diflufenzopyr in soil was approximately 8–10 d in the laboratory study and was less than four days under Canadian field conditions (Ontario), and was not considered to be persistent. Winter

cereals are the only crops that could be planted back at approximately five months from the latest possible date used to treat corn. Data for barley grain at the exaggerated 4× the Canadian proposed use rate, and at four-month plantback, indicated TRRs of <4 parts per billion (ppb).

Based on the above information, it appears unlikely that any residues of the parent compound and its metabolites will exceed 0.01 ppm in the rotational crops when corn is treated with diflufenzopyr at the Canadian rate of 57 g a.i./ha.

Environmental Chemistry and Fate
Environmental chemistry and fate studies indicated that biotransformation and hydrolysis in soil and water were the major transformation processes for diflufenzopyr.

The aerobic biotransformation in soil study, conducted in the laboratory, indicated that the half-life for the parent compound was approximately 8–10 d. For the pyridinyl-labelled parent compound, the major transformation products were M5 and M9. M1 was a minor transformation product. M9 persisted during the study (360 d). At the end of the study, M5 and M9 comprised 1.4% and 25% , respectively, of the initially applied radiolabel. Therefore M9 had a potential for carry-over to the next growing season under field conditions. For the phenyl-labelled parent compound, M5 was the only major transformation product. M5 reached a maximum concentration (19.5% of the initially applied radiolabel) at 14 d. CO_2 accounted for 35.1% and 33.5% of the initially applied radiolabel at 360 d post-application for the ^{14}C-pyridinyl- and phenyl-labelled parent compounds, respectively.

In the terrestrial field dissipation study (Canadian study), the half-life for diflufenzopyr was less than four days. Thus, diflufenzopyr did not appear to be persistent in soil. In the aerobic biotransformation soil metabolism study, M9 indicated a potential for carry-over. However, in the terrestrial field study conducted in Ontario, M9 was not detected (limit of detection [LOD] = 0.01 mg/L) in soil samples collected at the depth of 0–90 cm. Diflufenzopyr and M1 were not detected below the 15-cm soil depth.

Storage Stability
All the corn samples were analysed within 12 months. Storage stability data indicated that M1 and M10 were found to be stable in samples of corn silage, fodder and grain spiked at 0.1 ppm and stored at -12°C (10°F) for three to four months. An additional study to determine the stability of M1 and M10 in corn is in progress. Interim results showed that M1 was found to be stable in corn commodities for 14 months, and M10 was found to be stable in the same matrices for 18 months. No data on diflufenzopyr were available.

4.1.2 Definition of the residues in food of animal origin relevant to maximum residues limits

In the rat metabolism study, within 72 h of dosing, 20–44% of the radioactivity was excreted in the urine, while 49–79% of the radioactivity was excreted in the feces. Diflufenzopyr was excreted primarily as unchanged parent compound. Minor amounts of

hydrolysis products (M1, M5 and M6) and hydroxylation products (M9, M10 and M19) were identified in excreta.

The goat metabolism study indicated that diflufenzopyr was partially metabolized and rapidly eliminated from the animals. At feeding level of 10 ppm diflufenzopyr in the goat diet for four consecutive days, the maximum TRR was found in kidney at 0.113 ppm after goats were sacrificed within 24 h of the last dose. The TRRs were <0.01 ppm in muscle and 0.09 ppm in milk samples. Approximately 90% of the AD was excreted in urine and feces. In addition to the parent compound, the metabolites identified in goat urine, kidney, liver and milk were M1, M5, M6 and M19.

In the laying hen metabolism study, at a feeding level of 10 ppm for four consecutive days, 99% of the AD was eliminated in the excreta when hens were sacrificed within 24 h of the last dose, only 0.06–0.09% of the dose was found in the tissues and eggs. Data from excreta analysis indicated that 31.2–48.2% of the TRR was excreted as parent compound and 19.9–37.1% was M5. Minor metabolites M1, M6, M9, M10, and M19 were also identified in the excreta; however, none exceeded 10% of the TRR. The TRRs detected in most tissues were ≤0.006 ppm, except for ^{14}C-Phenyl liver, where the TRR was detected at a maximum level of 0.022 ppm and for ^{14}C-pyridine egg white, where the TRR was detected at a maximum level of 0.015 ppm. The TRRs in muscle were <0.005 ppm.

The anticipated residue levels in treated corn commodities were under the LOQ. The TRRs in all edible livestock commodities were ≤0.0005 ppm (0.5 ppb) when extrapolated from the 200× feeding level to the anticipated 1× feeding level; therefore, an animal feeding study was not required. Maximum residue limits would not be needed for meat, milk and eggs.

4.2 Residues relevant to consumer safety

The results of supervised field trials conducted in Eastern Canada indicated that when field corn was treated with diflufenzopyr at 1–2.8× the proposed rate, and harvested 60 d following application, no residues of M1 and M10 were detected above the LOQs of 0.01 ppm and 0.05 ppm, respectively, in corn forage. At harvest (post harvest interval 120 d), residues of M1 and M10 in corn fodder and grain were all under the LOQs.

The potential exposure of consumers to diflufenzopyr residues through dietary intake is very low. At the proposed recommended application rate of 57 g a.i./ha/season, residues of diflufenzopyr/M1 are not expected to occur in corn grain at levels greater than 0.02 ppm. A proposed MRL of 0.05 ppm (harmonized with that supported by the EPA) was used for corn grain and the 0.1-ppm general regulation level was used for animal tissues (a highly exaggerated residue level). Consumption statistics were used based on the *Apparent per Capita Domestic Consumption of Food in Canada,* 1996, and *USDA Continuing Survey of Food Intakes by Individuals,* 1996. Using these data, the potential daily intakes (PDI) were calculated for adults, infants and children and the PDIs were all below 4% of the ADI allotted to food. Ten percent of the ADI was allotted to drinking water.

The ADI was recommended at 0.26 mg/kg bw, based on the lowest NOEL of 26 mg/kg bw/d in the chronic rat study with a 100-fold safety factor.

4.3 Residue relevant to worker safety

Has been addressed in section 3.6.3.

4.4 Proposed maximum residue limits and compliance with existing maximum residue limits

4.4.1 Compliance with existing maximum residue limits

Since the active ingredient is new, there are no existing MRLs. The question of compliance with existing MRLs is not applicable.

4.4.2 Proposed maximum residue limits

On the basis of the results of supervised trials carried out in Eastern Canada, when corn is treated with diflufenzopyr according to the proposed label directions, the residues of diflufenzopyr equivalents in corn grain will not be expected to exceed 0.02 ppm. The EPA proposed a tolerance of 0.05 ppm in corn grain, forage and fodder. In the spirit of harmonization, a MRL of 0.05 ppm for corn grain has been proposed.

Since the anticipated residue levels in treated corn commodities were under the LOQ, an animal feeding study was not required. Maximum residue limits would not be needed for meat, milk and eggs.

5.0 Fate and behaviour in the environment

5.1 Fate and behaviour in soil

5.1.1 Phototransformation on soil

The half-life for phototransformation of diflufenzopyr on a soil surface was 14 d (total illumination). Phototransformation on soil is not expected to be a major route of transformation. Diflufenzopyr transformed to M5 and subsequently to M1. The product M6 was also a direct transformation product of the parent compound.

5.1.2 Aerobic soil biotransformation

The half-life of diflufenzopyr in soil was approximately 8–10 d. Based on this half-life, diflufenzopyr will not be persistent in soil under aerobic conditions. The major transformation product M9, however, persisted during the study and, thus, has a potential for carry-over to the next growing season.

5.1.3 Anaerobic soil biotransformation

An anaerobic soil biotransformation study was not submitted for review.

5.1.4 Field soil dissipation studies

One Canadian terrestrial field dissipation study on Distinct® was conducted. Based on a half-life of approximately four days, diflufenzopyr will not be persistent in soil. Although the aerobic soil biotransformation study indicated a potential for M9 to persist in soil, this major transformation product was not detected in the field study. The results from the adsorption study indicated a high to very high potential for leaching of diflufenzopyr and a low to moderate mobility for the transformation product M1. Diflufenzopyr and the transformation product M1 were not detected below 15 cm of soil in the terrestrial dissipation study and, thus, were not mobile under field conditions at the test site.

Field studies conducted in the U.S. used the active ingredient as the test material rather than the formulated product. Studies conducted in California and Nebraska would not be considered relevant to Canada as the climatic conditions are not similar to those in the corn growing regions of Eastern Canada.

5.1.5 Mobility: soil adsorption/desorption studies

The adsorption constants (K_{oc} values ranged from 18 to 156) indicated that diflufenzopyr has a high to very high potential for mobility. The relatively high K_{oc} value for the silt loam soil was attributed to the high rate of transformation that occurred in this soil.

The adsorption constants for M1 (K_{oc} values ranged from 140 to 596) indicated that this transformation product has a low to medium potential for mobility in the loamy soils, except in the soil with a high sand content. The transformation product, M9, (K_{oc} values 385–826) has a low to medium potential for mobility, except for soil with a high sand content (K_{oc} = 3668) for which there is a high potential for mobility.

5.1.6 Mobility: soil column leaching

A soil column leaching study was not submitted for review.

5.1.7 Mobility: soil thin layer chromatography

A soil thin layer chromatography study was not submitted for review.

5.1.8 Mobility: field leaching data

A field leaching study was not submitted for review.

5.1.9 Expected environmental concentrations in soil

The expected concentration of diflufenzopyr in a 15-cm depth of soil that would result from one application at the maximum rate of application of 57 g/ha is 0.025 mg/kg soil.

5.2 Fate and behaviour in aquatic systems

5.2.1 Hydrolysis

The rate of hydrolysis was pH-dependent. The half-life values, based on first-order kinetics, were 12.9, 23.9 and 25.6 d for pH 5, pH 7 and pH 9, respectively. The major transformation products were M1 and M6 (at pH 5 only). The potential for persistence of these compounds in aqueous environments was not determined.

5.2.2 Phototransformation in water

Phototransformation in water was pH dependent. The half-lives were 6.8, 16.8 and 13.4 d (total illumination) at pH 5, pH 7 and pH 9, respectively. Phototransformation in water is not considered to be a significant process for transformation of diflufenzopyr.

5.2.3 Aquatic aerobic biotransformation

The half-life for aerobic aquatic biotransformation of SAN 835H was 26 and 25 d for the phenyl- and pyridinyl-labelled diflufenzopyr, respectively. SAN 835H transformed to the phenyl and phthalazinone residues, M1 and M2, respectively. Subsequently, M2 transformed to M9, and M9 transformed to M6. Minor transformation products derived from M1, M2 and M9 were also detected.

The partitioning of the parent compound and the major transformation products, M1 and M9, in the water/sediment system can be predicted from the results of the adsorption/desorption studies. As SAN 835H has a high to very high potential for mobility in soil, it would be expected to have a low potential for binding to sediment. The major transformation products, M1 and M9, have a low to medium potential for mobility in soil and, thus, they would be expected to have a higher potential for binding to sediment.

Under aerobic aquatic conditions, diflufenzopyr will not persist; however, the transformation product, M9, has a potential to persist.

5.2.4 Aquatic anaerobic biotransformation

The major transformation products that were detected in the water/sediment system with pyridinyl-labelled SAN 836H were M1 and M9. The major transformation product with the phenyl label was M2. M9 has a potential for persistence in water and in sediment.

The half-life for SAN 836H was approximately 20–26 d. Decline time 90% (DT_{90}) values were not reported. Based on the half-life values, diflufenzopyr is not persistent under anaerobic aquatic conditions.

5.2.5 Expected environmental concentration in surface water

The expected concentration of diflufenzopyr in a 30-cm water column that would result from a single direct overspray at the maximum rate of application of 57 g/ha is 0.019 mg/L.

Run-off into shallow bodies of water (i.e., small ponds and fish spawning streams) was calculated using a scenario with a 100-ha watershed and a pond area of one hectare. For water-soluble pesticides applied as aqueous solutions, a percentage run-off rate of 0.5% is employed. The concentration of diflufenzopyr in a 30-cm water column that would result from a single application at the maximum rate of 57 g/ha is 0.0095 mg/L.

6.0 Effects on non-target species

6.1 Effects on terrestrial non-target species

The toxicity endpoints for the non-target species tested are summarized in Tables 6.1 and 6.2.

Table 6.1 Toxicity to non-target species

SPECIES	TOXICITY
earthworms (*Eisenia foetida*)	14-d LC_{50} >1000 mg/kg soil 14-d no observed effect concentration (NOEC) = 500 mg/kg/soil
honey bees (*Apis mellifera*)	48-h LD_{50} >25 µg acid equivalent (A.E.)/bee 48-h NOEC = 25 µg A.E./bee relatively non-toxic
daphnia (*Daphnia magna*)	48-h LC_{50} = 15.0 mg/L 48-h NOEC = 9.7 mg/L slightly toxic
mysid shrimp (*Mysidopsis bahia*)	96-h LC_{50} = 18.9 mg/L 96-h NOEC = 4.4 mg/L slightly toxic
oyster (*Crassostrea virginica*)	96-h Effect concentration (EC_{50}) = 61 mg/L 96-h NOEC = 31 mg/L slightly toxic ~ 20% inhibition of growth at lowest test concentration could be biologically significant

SPECIES	TOXICITY
bluegill sunfish (*Lepomis machrochirus*)	96-h LC_{50} >135 mg/L 96-h NOEC = 16 mg/L practically non-toxic
rainbow trout (*Oncorhynchus mykiss*)	96-h LC_{50} = 106 mg/L 96-h NOEC = 80 mg/L practically non-toxic inappropriate test range
sheepshead minnow (*Cyprinodon variegatus*)	96-h LC_{50} >138 mg/L 96-h NOEC = 138 mg/L practically non-toxic
bobwhite quail (*Colinus virginianus*) - acute	14-d LD_{50} >1868 mg/kg bw 14-d NOEC = 1868 mg/kg bw slightly toxic adjusted values based on 82% purity of test material
bobwhite quail (*Colinus virginianus*) - dietary	8-d LD_{50} >4608 mg/kg feed 8-d NOEC = 4608 mg/kg feed slightly toxic adjusted values due to purity of test material
mallard duck (*Anas platyrhynchos*) - dietary	8-d LC_{50} >4608 mg/kg feed 8-d NOEC = 2591 mg/kg feed slightly toxic adjusted values due to purity of test material
bluegreen alga (*Anabaena flos-aquae*) -active ingredient	5-d EC_{50} = 0.15 mg A.E./L 5-d NOEC = 0.014 mg A.E./L
bluegreen alga (*Anabaena flos-aquae*) - formulation	5-d EC_{50} >0.26 mg A.E./L 5-d NOEC = 0.0059 mg A.E./L
bluegreen alga (*Selenastrum capricornutum*)	5-d EC_{25} = 0.024 mg A.E./L 5-d EC_{50} = 0.11 mg A.E./L 5-d NOEC = 0.0078 mg A.E./L
freshwater diatom (*Navicula pelliculosa*)	5-d EC_{25} = 0.014 mg A.E./L 5-d EC_{50} = 0.10 mg A.E./L 5-d NOEC = 0.003 mg A.E./L
marine diatom (*Skeletoneum costatum*)	5-d EC_{25} = 0.031 mg A.E./L 5-d EC_{50} = 0.12 mg A.E./L 5-d NOEC = 0.0064 mg A.E./L

SPECIES	TOXICITY
duckweed (*Lemna gibba*) - active ingredient	14-d EC_{50} >0.35 mg A.E./L 14-d NOEC = 0.0039 mg/L
duckweed (*Lemna gibba*) - formulation	14-d EC_{25} = 0.0029 mg A.E./L 14-d EC_{50} = 0.11 mg A.E./L 14-d NOEC = 0.0023 mg A.E./L
terrestrial plants - active ingredient germination emergence vegetative vigour	 EC_{25} = 0.0008 lb/acre turnip shoot length (0.896 g/ha) Study invalid
terrestrial plants - formulation emergence vegetative vigour	 EC_{25} = 0.0043 lb/A turnip shoot length (4.82 g/ha) Study invalid

Table 6.2 Toxicity to mammals

Study	Species Tested	Value
acute oral	SD rat (a.i.) SD rat (formulated product)	LD_{50} >5.0 g/kg bw low acute toxic by oral route LD_{50} = 1.8 g/kg bw slightly acutely toxic by oral route
dietary	CD-1 mouse Wistar rat	NOEL = 7000 mg/kg feed NOEL = 5000 mg/kg feed
reproduction	Wistar rat	NOEL = 2000 mg/kg feed
teratogenicity	Wistar rat NZW rabbit	NOEL = 1000 mg/kg feed NOEL = 300 mg/kg feed

6.1.1 Birds

The expected concentration of diflufenzopyr in the diet of the bobwhite quail and the mallard duck is 4.73 and 1.93 mg/kg dry weight (dw), respectively. These values were calculated using a rate of application of 57 g diflufenzopyr/ha to determine the residue on various food sources and the percentage of these food sources in the diet of each species.

There were no mortalities or adverse clinical signs in the acute toxicity with bobwhite quail. The reported NOEC and LD_{50} values were 2250 mg a.i./kg bw and >2250 mg a.i./kg bw, respectively. The values should be 1868 mg a.i./kg bw and >1868 mg a.i./kg bw, respectively. SAN 835H is slightly toxic to bobwhite quail.

No mortalities or adverse clinical signs were reported in the dietary study with the bobwhite quail. The reported NOEC and LC_{50} values were 4608 mg a.i./kg feed and >4608 mg a.i./kg feed, respectively. SAN 835H is slightly toxic to bobwhite quail on a dietary basis. For the dietary study with the mallard duck, no mortalities or adverse clinical signs were reported. The NOEC and LC_{50} values were 2591 mg a.i./kg feed and >4608 mg a.i./kg feed, respectively. SAN 835H is slightly toxic to the mallard duck on a dietary basis.

6.1.2 Wild mammals

The expected concentration of diflufenzopyr in the diet of the rat, mouse and rabbit were calculated to be 28.76, 41.35 and 50.53 mg/kg dw, respectively. These values were calculated using a rate of application of 57 g diflufenzopyr/ha to determine the residue on various food sources and the percentage of these food sources in the diet of each species. For SD rats, the technical active ingredient and the formulated product had a low acute oral toxicity and a slight acute oral toxicity, respectively. The most sensitive indicator of effects of diflufenzopyr was the NOEL (300 mg/kg bw) for teratogenicity in NZW rabbits.

6.1.3 Bees

The acute toxicity study with honey bees was conducted as a maximum challenge test and, thus, estimated 48-h NOEC and LD_{50} were determined to be >25 µg A.E./bee. Based on these values, diflufenzopyr is relatively non-toxic to honey bees.

6.1.4 Arthropod predators and parasites

Studies on arthropod predators and parasites were not submitted for review.

6.1.5 Effects on earthworms and other soil macro-organisms

The 14-d LC_{50} and NOEC for earthworms were >1,000 mg/kg dw soil and 500 mg a.i./kg dw soil, respectively. The expected concentration of diflufenzopyr in soil is 0.025 mg/kg dw soil. Consequently, diflufenzopyr is not expected to have acute

adverse effects on earthworms following a single application at the maximum rate of application.

6.1.6 Effects on soil micro-organisms

Studies of the effects on soil micro-organisms were not submitted for review.

6.1.7 Non-target plants

The effects of diflufenzopyr on terrestrial plants were examined using seed gemination, seedling emergence and vegetative vigour. Based on the EC_{25} and the NOEC values, radical length was a more sensitive indicator than percentage germination for the seed germination test. Based on the EC_{25}, the most sensitive species was cabbage. Corn and lettuce were the least sensitive. Based on the EC_{25} and NOEC values, lettuce was the most sensitive species in the seedling emergence study. Shoot length was a more sensitive parameter than percentage emergence. Based on the EC_{25} values, root weight was the most sensitive parameter for cabbage, cucumber, lettuce, perennial ryegrass, soybean and tomato. Shoot weight was the most sensitive parameter for onion and turnip. For oat and corn, all three parameters had the same value. The most sensitive species was turnip. The vegetative study was considered to be invalid and a new study was requested.

The toxicity endpoint of SAN 1269H for the bluegreen alga, *Anabaena flos-aquae*, and duckweed, *Lemna gibba,* are summarized in Table 6.1. The EC_{50} for these species are greater than the expected environmental concentration (EEC) in water (0.10 mg A.E./L) and the NOECs are less than the EEC. For terrestrial plants treated with SAN 1269H, seedling emergence and vegetative vigour tests were conducted. The EC_{25} values for seedling emergence indicated that shoot length was a more sensitive parameter than percentage emergence. Lettuce was the most sensitive species. For vegetative vigour with cabbage, cucumber, lettuce and tomato, shoot weight was the most sensitive indicator, whereas, shoot length was the most sensitive for soybean. All three parameters had the same EC_{25} values for corn and oat. Turnip was the most sensitive species. The vegetative study was considered to be invalid and a new study was requested.

6.2 Effects on non-target aquatic species

6.2.1 Fish bioconcentration study

A study on bioconcentration in fish was not submitted for review. Based on the very low K_{ow} for diflufenzopyr, it is not anticipated that it will bioconcentrate in fish.

6.2.2 Aquatic invertebrates

The 48-h LC_{50} and NOEC for daphnids (*Daphnia magna*) were 15.0 and 9.7 mg a.i./L, respectively. Diflufenzopyr is classified as slightly toxic to daphnids. The reported 96-h LC_{50} and 96-h NOEC mysid shrimp *(Mysidopsis bahia)* were 18.9 and 4.4 mg a.i./L, respectively. Diflufenzopyr is classified as slightly toxic to mysid shrimp.

The reported 96-h EC_{50} and NOEC for oysters (*Crassostrea virginica*) were 61 and 31 mg a.i./L, respectively. The 96-h EC_{50} and NOEC were 61 and 31 mg a.i./L, respectively. Diflufenzopyr is slightly toxic to oysters. Although not considered to be statistically significant, the 19.9% inhibition of shell growth at the lowest test concentration may be biologically significant. As the EEC in water is 0.019 mg SAN 835H/L, it is not expected that diflufenzopyr will affect mollusc shell growth.

6.2.3 Fish

The 96-h LC_{50} and 96-h NOEC for bluegill sunfish (*Lepomis machrochirus*) were >135 mg a.i./L and 16 mg a.i./L, respectively. The LC_{50} of >135 mg a.i./L indicated that diflufenzopyr is classified as practically non-toxic to bluegill sunfish. For rainbow trout (*Oncorhynchus mykiss*), the reported 96-h LC_{50} was 106 mg/L and the NOEC was 80 mg/L. Based on the 96-h LC_{50}, diflufenzopyr is classified as practically non-toxic to rainbow trout. The 96-h LC_{50} and NOEC for sheepshead minnow (*Cyprindon variegatus*) were >138 mg/L. The LC_{50} indicated that SAN 835H is classified as practically non-toxic to sheepshead minnow.

6.2.4 Algae

The EC_{50} and NOEC values for freshwater bluegreen algae *(Anabaena flos-aquae)* were 0.15 mg A.E./L and 0.014 mg A.E./L, respectively. The NOEC is slightly less than the EEC in water.

For the freshwater bluegreen algae (*Selenastrum capricornutum*), the five-day EC_{25}, EC_{50} and NOEC were 0.024, 0.11 and 0.0078 mg A.E./L. The EC_{50} is less than the EEC in water (0.019 mg SAN 836H/L). The NOEC is approximately 2.4 times less than the EEC.

The five-day NOEC, EC_{25} and EC_{50} values for the freshwater diatom, (*Navicula pelliculosa*) were 0.003, 0.014 and 0.10 mg A.E./L, respectively. The EEC in water is approximately 6.3 times greater than the NOEC. For the marine diatom (*Skeletonema costatum*), the 96-h EC_{25}, EC_{50} and NOEC were 0.031, 0.14 and 0.0064 mg A.E. SAN 836H/L, respectively. The EEC in water (0.019 mg a.i./L) is approximately three times greater than the NOEC.

6.2.5 Aquatic plants

For the study conducted with the active ingredient, the reported EC_{50} and NOEC for duckweed (*Lemna gibba*) were >0.35 and 0.0039 mg A.E./L, respectively. As the expected concentration of diflufenzopyr in water at a depth of 30 cm is 0.019 mg/L, there is a potential for adverse affects on duckweed. For the duckweed toxicity study conducted with the diflufenzopyr and dicamba mixture (SAN 1269H), biomass was the most sensitive indicator. The EC_{25} and EC_{50} values were 0.0029 and 0.11 mg A.E. SAN 1269H/L respectively. The 14-d NOEC was 0.0023 mg A.E. SAN 1269H/L.

6.3 Effects on biological methods of sewage treatment

These studies are not required under the Canadian regulatory system.

6.4 Environmental risk assessment

6.4.1 Terrestrial organisms

a) Earthworms

The NOEC for the earthworm (*Eisenia foetida*) (500 mg diflufenzopyr/kg soil) was 20×10^4 times greater than the EEC of diflufenzopyr in soil (0.025 mg/kg soil). Consequently, diflufenzopyr will not have an adverse effect on earthworms.

b) Honeybee

Diflufenzopyr is classified as relatively non-toxic to honey bees. Consequently, it is not anticipated that diflufenzopyr will have adverse effects on honey bees.

c) Wild birds

The 14-d LD_{50} and 14-d NOEC derived from the results of the acute toxicity study conducted with the bobwhite quail were >1868 and 1868 mg/kg bw, respectively. Using an average body weight of 170 g and a daily intake of 15.2 g of food, the reviewer calculated that the maximum number of days of intake by a bobwhite quail equivalent to the dose administered by gavage that had no observable effect on the laboratory population would be 4.4×10^3 d.

The 8-d LC_{50} and 8-d NOEC that were derived from the results of the dietary study with the bobwhite quail were >4608 and 4608 mg/kg feed, respectively. The risk quotient and the safety factor based on the NOEC were calculated to be 1.03×10^{-3} and 9.74×10^2, respectively.

For the dietary study with the mallard duck, the 8-d LC_{50} and 8-d NOEC were >4608 and 2519 mg/kg feed, respectively. The risk quotient and the safety factor based on the NOEC were calculated to be 4.19×10^{-4} and 1.34×10^3, respectively.

Based on these values, it is anticipated that birds exposed to residues on food sources that would result from a single treatment of diflufenzopyr at the application rate of 57 g/ha will not be at risk of adverse effects.

d) Wild mammals

Results from the acute oral toxicity studies indicated that the maximum number of days of intake of diflufenzopyr by a wild SD rat equivalent to the dose administered by gavage that had no observable effect on the laboratory population would be 196 and 185 d for male and female rats, respectively. The corresponding value for the formulated product was 70 d for males and 67 d for female rats, respectively. Therefore, there is no risk to rats from oral exposure to diflufenzopyr.

Safety factors were calculated using the endpoint values from dietary and reproductive studies (Table 6.3).

Table 6.3 Safety factors based on dietary and reproductive studies.

Study	Species Tested	SF (NOEC/EEC)
dietary	CD-1 mouse Wistar rat	169 121
reproduction	Wistar rat	48
teratogenicity	Wistar rat NZW rabbit	24 6

6.4.2 Aquatic organisms

The bluegill sunfish was the most sensitive species of fish. The 96-h NOEC for bluegill sunfish, 16 mg/L, is 842 times greater than the EEC in a 30-cm column of water that would result from a direct overspray. Consequently, fish are not expected to be adversely affected from a single treatment of diflufenzopyr at the application rate of 56 g/ha.

The 48-h NOEC for mysid shrimp, 4.4 mg/L, is 232 times greater than the EEC in a 30-cm column of water that would result from a direct overspray. Consequently, aquatic invertebrates are not expected to be adversely affected from a single treatment of diflufenzopyr at the application rate of 57 g/ha.

The five-day NOEC values for the fresh water bluegreen algae, *Anabaena flos-aquae* and *Selenastrum capricornutum*, were 0.014 and 0.0078 mg/L, respectively. For the freshwater diatom, *Navicula pelliculosa*, and duckweed, *Lemna gibba*, the five-day NOEC values were 0.003 and 0.0039 mg/L, respectively. These values are less than the EEC of diflufenzopyr in water (0.019 mg/L); therefore, there is a potential for adverse impact on these species.

The NOEC values for the bluegreen algae, *Selenastrum capricornutum* (0.0078 mg/L), the freshwater diatom, *Navicula pelliculosa* (0.003 mg/L), and duckweed, *Lemna gibba* (0.0039 mg/L), are less than the EEC resulting from run-off (0.0095 mg/L). Consequently, there is a potential for adverse effects from diflufenzopyr from run-off into shallow ponds.

For the formulated product, the five-day NOEC for the fresh water bluegreen algae, *Anabaena flos-aquae*, and duckweed, *Lemna gibba*, were 0.0059 and 0.0039 mg A.E./L, respectively. These values are less than the EEC of diflufenzopyr in water (0.067 mg active ingredients/L); therefore, there is a potential for adverse impact on these species.

6.5 Environmental risk mitigation

Aquatic buffer zones
Based on a model using the results from Norby and Skuterud (1975) and using the 14-d NOEC (0.0023 mg/L) for the most sensitive species, *Lemna gibba*, a buffer zone of one metre is required to protect aquatic organisms.

Terrestrial buffer zones
Based on the EC_{25} (formulated product) for turnips, a buffer zone of 16 m is required for the protection of sensitive terrestrial habitats (e.g., shelterbelts).

7.0 Efficacy data and information

7.1 Effectiveness

7.1.1 Intended use

Diflufenzopyr is a selective, pre-emergence and post-emergence herbicide that controls broadleaf weeds in field corn. This new active ingredient is efficacious at low use rates. Diflufenzopyr will be commercialized as a pre-mix product with dicamba, an active ingredient that is currently registered in Canada. The commercial name for the diflufenzopyr + dicamba product is Distinct®. Distinct® contains 20% diflufenzopyr and 50% dicamba providing an overall guarantee of 70% active ingredient.

Distinct® may be used for pre-emergent, spike stage (spike–1 leaf), early post-emergent (2–3 leaf) and late post-emergent (4–6 leaf) application on field corn in Eastern Canada. Distinct® is not for use on sweet corn or seed corn. An application of Distinct® at the above-stated timings relative to the crop, except for pre-emergent where the tankmix with dimethenamid is recommended, is effective in controlling the following broadleaf weeds: redroot pigweed, common ragweed, lamb's-quarters, wild buckwheat, lady's thumb and velvetleaf (velvetleaf controlled with post-emergent application only). When applied at the early or late post-emergent treatment, a non-ionic surfactant at 0.25% v/v and liquid urea ammonium nitrate at 1.25% v/v must be used.

Distinct® can be tankmixed with dimethenamid at a rate of 1.125 kg a.i./ha for control of the above broadleaf weeds in addition to the following annual grass weeds: green foxtail, yellow foxtail, crabgrass, old witchgrass, barnyard grass and fall panicum.

7.1.2 Mode of action

Diflufenzopyr is an auxin transport inhibitor. Diflufenzopyr inhibits the polar transport of naturally occurring auxins (indoleacetic acid [IAA]) and synthetic auxin-like compounds, such as dicamba, in sensitive plants. Diflufenzopyr's inhibition of auxin transport causes abnormal accumulation of IAA and synthetic auxin agonists in meristematic shoot and root regions, disrupting the delicate auxin balance needed for plant growth. When diflufenzopyr is applied with dicamba, as in the Distinct®

formulated product, it focuses dicamba's translocation to the meristematic sinks, where it delivers effective weed control at reduced rates. Sensitive broadleaf weeds exhibit rapid and severe plant hormonal effects (e.g., epinasty) after application of Distinct.® Symptoms are visible within hours and plant death usually occurs within a few days.

Tolerance in field corn occurs through rapid metabolism of diflufenzopyr and dicamba.

7.1.3 Crops

Field corn is the only crop on which data is presented and for which a label claim is made.

7.1.4 Effectiveness against pests

Efficacy of Distinct® applied alone and tankmixed with dimethenamid was studied in a total 72 trials conducted over four growing seasons, from 1994 to 1997. A summary of the number of trials submitted in support of each weed for each time of application is presented below.

Table 7.1 Summary of the number of trials submitted for each weed claim over the various application timings, Distinct® alone

Weed	Number of Trials per Application Timing			Total Number of Trials
	Spike	Early Post-emerge	Late Post-emerge	
Redroot pigweed	12	17	17	46
Lamb's-quarters	14	16	19	49
Common ragweed	7	8	10	25
Wild buckwheat	3	5	8	16
Lady's thumb	4	6	9	19
Velvetleaf	6	3	4	13

Table 7.2 Summary of the number of trials submitted for each weed claim over the various application timings, Distinct® + dimethenamid tankmix

Weed	Number of Trials per Application Timing			Total Number of Trials
	Pre-emerge	Spike	Early Post-emerge	
Redroot pigweed	11	12	8	31
Lamb's-quarters	14	14	8	36
Common ragweed	5	7	4	16
Wild buckwheat	3	3	1	7
Lady's thumb	3	4	3	10
Velvetleaf	-	6	3	9
Green foxtail	8	8	8	24
Yellow foxtail	4	3	-	7
Crabgrass	5	5	5	15
Barnyard grass	5	6	6	17
Fall panicum	3	2	2	7
Old witchgrass	-	2	1	3

Distinct® applied alone was evaluated for annual broadleaf weed control. The Distinct® + dimethenamid tankmix was evaluated for annual grass and broadleaf weed control to ensure control of these weeds was not compromised when Distinct® is applied in a tankmix with dimethenamid. The following results were obtained.

7.1.4.1 Pre-emergent application

Distinct® 0.200 kg a.i./ha + dimethenamid 1.125 kg a.i./ha

Redroot pigweed (*Amaranthus retroflexus*)
Control of redroot pigweed was reported in 11 trials conducted over three years over 11 locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 95% (number of trials [n] = 11) at 14–41 days after application (DAA) and 90% (n = 7) at 41 or more DAA.

Lamb's-quarters (*Chenopodium album*)
Control of lamb's-quarters was reported in 14 trials conducted over three years over 12 locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 93% (n = 14) at 14–41 DAA and 92% (n = 11) at 41 or more DAA.

Common ragweed (*Ambrosia artemisiifolia*)
Control of common ragweed was reported in five trials conducted over three years over five locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 97% (n = 5) at 14–41 DAA and 91% (n = 2) at 41 or more DAA.

Wild buckwheat (*Polygonum convolvulus*)
Control of wild buckwheat was reported in three trials conducted over three years over three locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 89% (n = 2) at 14–41 DAA and 86% (n = 3) at 41 or more DAA.

Lady's thumb (*Polygonum persicaria*)
Control of lady's thumb was reported in three trials conducted over one year over three locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 90% (n = 1) at 14–41 DAA and 88% (n = 2) at 41 or more DAA.

Green foxtail (*Setaria viridis*)
Control of green foxtail was reported in eight trials conducted over three years over seven locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 99% (n = 8) at 14–41 DAA and 98% (n = 6) at 41 or more DAA. The average control for an application of dimethenamid alone was 98% (n = 8) at 14–41 DAA and 99% (n = 6) at 41 or more DAA. The level of control provided by dimethenamid for this grass weed was not compromised when tankmixed with Distinct®.

Yellow foxtail (*Setaria glauca*)
Control of yellow foxtail was reported in four trials conducted over two years over four locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 95% (n = 3) at 14–41 DAA and 76% (n = 3) at 41 or more DAA. The average control for an application of dimethenamid alone was 91% (n = 3) at 14–41 DAA and 69% (n = 3) at 41 or more DAA. The level of control provided by dimethenamid for this grass weed was not compromised when tankmixed with Distinct®.

Crabgrass (*Digitaria sanguinalis*)
Control of crabgrass was reported in five trials conducted over two years over four locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 99% (n = 2) at 14–41 DAA and 98% (n = 4) at 41 or more DAA. The average control for an application of dimethenamid alone was

99% (n = 2) at 14–41 DAA and 98% (n = 4) at 41 or more DAA. The level of control provided by dimethenamid for this grass weed was not compromised when tankmixed with Distinct®.

Barnyard grass (*Echinochloa crusgalli*)
Control of barnyard grass was reported in five trials conducted over three years over five locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 99% (n = 4) at 14–41 DAA and 99% (n = 4) at 41 or more DAA. The average control for an application of dimethenamid alone was 96% (n = 4) at 14–41 DAA and 99% (n = 4) at 41 or more DAA. The level of control provided by dimethenamid for this grass weed was not compromised when tankmixed with Distinct®.

Fall panicum (*Panicum dichotomiflorum*)
Control of fall panicum was reported in three trials conducted over two years over three locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 91% (n = 2) at 14–41 DAA and 88% (n = 3) at 41 or more DAA. The average control for an application of dimethenamid alone was 92% (n = 2) at 14–41 DAA and 98% (n = 3) at 41 or more DAA. The level of control provided by dimethenamid for this grass weed was not compromised when tankmixed with Distinct®.

7.1.4.2 Spike stage application

a) Distinct® at 0.200 kg a.i./ha alone

Redroot pigweed (*Amaranthus retroflexus*)
Control of redroot pigweed was reported in 12 trials conducted over three years over 10 locations across Ontario and Quebec. The average control for an application of Distinct® alone was 90% (n = 11) at 14–41 DAA and 83% (n = 7) at 41 or more DAA.

Lamb's-quarters (*Chenopodium album*)
Control of lamb's-quarters was reported for 14 trials conducted over three years over 10 locations across Ontario and Quebec. The average control for an application of Distinct® alone was 87% (n = 12) at 14–41 DAA and 76% (n = 9) at 41 or more DAA. Due to the inconsistent control of lamb's-quarters later in the growing season when treated with Distinct® alone, the label will recommend the use of the Distinct® + dimethenamid tankmix when heavy populations of lamb's-quarters are present.

Common ragweed (*Ambrosia artemisiifolia*)
Control of common ragweed was reported in seven trials conducted over three years over six locations across Ontario and Quebec. The average control for an application of Distinct® alone was 96% (n = 6) at 14–41 DAA and 94% (n = 3) at 41 or more DAA.

Wild buckwheat (*Polygonum convolvulus*)
Control of wild buckwheat was reported in three trials conducted over three years over two locations across Ontario and Quebec. The average control for an application of Distinct® alone was 88% (n = 2) at 14–41 DAA and 92% (n = 2) at 41 or more DAA.

Lady's thumb (*Polygonum persicaria*)
Control of lady's thumb was reported in four trials conducted over two years over four locations across Ontario and Quebec. The average control for an application of Distinct® alone was 94% (n = 4) at 14–41 DAA and 94% (n = 2) at 41 or more DAA.

b) Distinct® at 0.200 kg a.i./ha + dimethenamid at 1.125 kg a.i./ha

Redroot pigweed (*Amaranthus retroflexus*)
Control of redroot pigweed was reported in 12 trials conducted over three years over 10 locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 98% (n = 12) at 14–41 DAA and 97% (n = 8) at 41 or more DAA.

Lamb's-quarters (*Chenopodium album*)
Control of lamb's-quarters was reported in 14 trials conducted over three years over 10 locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 98% (n = 14) at 14–41 DAA and 94% (n = 11) at 41 or more DAA.

Common ragweed (*Ambrosia artemisiifolia*)
Control of common ragweed was reported in seven trials conducted over three years over six locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 98% (n = 7) at 14–41 DAA and 94% (n = 4) at 41 or more DAA.

Wild buckwheat (*Polygonum convolvulus*)
Control of wild buckwheat was reported in three trials conducted over three years over two locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 96% (n = 3) at 14–41 DAA and 95% (n = 3) at 41 or more DAA.

Lady's thumb (*Polygonum persicaria*)
Control of lady's thumb was reported in four trials conducted over two years over four locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 98% (n = 3) at 14–41 DAA and 99% (n = 2) at 41 or more DAA.

Green foxtail (*Setaria viridis*)
Control of green foxtail was reported in eight trials conducted over three years over six locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 98% (n = 8) at 14–41 DAA and 96% (n = 6) at 41 or more DAA. The average control for an application of dimethenamid alone was

94% (n = 7) at 14–41 DAA and 96% (n = 6) at 41 or more DAA. The level of control provided by dimethenamid for this grass weed was not compromised when tankmixed with Distinct®.

Yellow foxtail (*Setaria glauca*)
Control of yellow foxtail was reported in three trials conducted over two years over three locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 99% (n = 3) at 14–41 DAA and 96% (n = 2) at 41 or more DAA. The average control for an application of dimethenamid alone was 99% (n = 1) at 14–41 DAA and 95% (n = 1) at 41 or more DAA. The level of control provided by dimethenamid for this grass weed was not compromised when tankmixed with Distinct®.

Crabgrass (*Digitaria sanguinalis*)
Control of crabgrass was reported in five trials conducted over two years over four locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 96% (n = 5) at 14–41 DAA and 94% (n = 3) at 41 or more DAA. The average control for an application of dimethenamid alone was 93% (n = 5) at 14–41 DAA and 95% (n = 3) at 41 or more DAA. The level of control provided by dimethenamid for this grass weed was not compromised when tankmixed with Distinct®.

Barnyard grass (*Echinochloa crusgalli*)
Control of barnyard grass was reported in six trials conducted over three years over six locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 99% (n = 6) at 14–41 DAA and 99% (n = 4) at 41 or more DAA. The average control for an application of dimethenamid alone was 99% (n = 3) at 14–41 DAA and 99% (n = 4) at 41 or more DAA. The level of control provided by dimethenamid for this grass weed was not compromised when tankmixed with Distinct®.

Fall panicum (*Panicum dichotomiflorum*)
Control of fall panicum was reported in two trials conducted over two years over two locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 90% (n = 1) at 14–41 DAA and 94% (n = 2) at 41 or more DAA. The average control for an application of dimethenamid alone was 76% (n = 1) at 14–41 DAA and 92% (n = 2) at 41 or more DAA. The level of control provided by dimethenamid for this grass weed was not compromised when tankmixed with Distinct®.

Old witchgrass (*Panicum capillare*)
Control of old witchgrass was reported in two trials conducted over one year over two locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 99% (n = 1) at 14–41 DAA and 99% (n = 2) at 41 or more DAA. The average control for an application of dimethenamid alone was 98% (n = 1) at 14–41 DAA and 99% (n = 1) at 41 or more DAA. The level of control

provided by dimethenamid for this grass weed was not compromised when tankmixed with Distinct®.

7.1.4.3 Early post-emerge application (2- to 3-leaf stage of the corn crop)

a) Distinct® at 0.200 kg a.i./ha alone

Redroot pigweed (*Amaranthus retroflexus*)
Control of redroot pigweed was reported in 17 trials conducted over two years over 12 locations across Ontario and Quebec. The average control for an application of Distinct® alone was 96% (n = 17) at 14–41 DAA and 89% (n = 12) at 41 or more DAA.

Lamb's-quarters (*Chenopodium album*)
Control of lamb's-quarters was reported in 16 trials conducted over two years over 11 locations across Ontario and Quebec. The average control for an application of Distinct® alone was 95% (n = 16) at 14–41 DAA and 91% (n = 14) at 41 or more DAA.

Common ragweed (*Ambrosia artemisiifolia*)
Control of common ragweed was reported in eight trials conducted over two years over six locations across Ontario and Quebec. The average control for an application of Distinct® alone was 99% (n = 8) at 14–41 DAA and 98% (n = 3) at 41 or more DAA.

Wild buckwheat (*Polygonum convolvulus*)
Control of wild buckwheat was reported in five trials conducted over two years over three locations across Ontario and Quebec. The average control for an application of Distinct® alone was 98% (n = 4) at 14–41 DAA and 97% (n = 4) at 41 or more DAA.

Lady's thumb (*Polygonum persicaria*)
Control of lady's thumb was reported in six trials conducted over two years over four locations across Ontario and Quebec. The average control for an application of the Distinct® alone was 97% (n = 6) at 14–41 DAA and 99% (n = 4) at 41 or more DAA.

Velvetleaf (*Abutilon theophrasti*)
Control of velvetleaf was reported in three trials conducted over two years over two locations across Ontario and Quebec. The average control for an application of the Distinct® alone was 85% (n = 3) at 14–41 DAA and 83% (n = 3) at 41 or more DAA.

b) Distinct® at 0.200 kg a.i./ha + dimethenamid at 1.125 kg a.i./ha

Redroot pigweed (*Amaranthus retroflexus*)
Control of redroot pigweed was reported in eight trials conducted over two years over six locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 98% (n = 8) at 14–41 DAA and 96% (n = 5) at 41 or more DAA.

Lamb's-quarters (*Chenopodium album*)
Control of lamb's-quarters was reported in eight trials conducted over two years over six locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 98% (n = 8) at 14–41 DAA and 97% (n = 6) at 41 or more DAA.

Common ragweed (*Ambrosia artemisiifolia*)
Control of common ragweed was reported in four trials conducted over one year over three locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 99% (n = 4) at 14–41 DAA and 99% (n = 3) at 41 or more DAA.

Wild buckwheat (*Polygonum convolvulus*)
Control of wild buckwheat was reported in one trial. The average control for an application of the Distinct® + dimethenamid tankmix was 99% (n = 1) at 14–41 DAA and 99% (n = 1) at 41 or more DAA.

Lady's thumb (*Polygonum persicaria*)
Control of lady's thumb was reported in three trials conducted over one year over three locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 98% (n = 3) at 14–41 DAA and 99% (n = 1) at 41 or more DAA.

Velvetleaf (*Abutilon theophrasti*)
Control of velvetleaf was reported in three trials conducted over two years over two locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 83% (n = 3) at 14–41 DAA and 81% (n = 3) at 41 or more DAA.

Green foxtail (*Setaria viridis*)
Control of green foxtail was reported in eight trials conducted over two years over five locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 97% (n = 4) at 14–41 DAA and 94% (n = 3) at 41 or more DAA. The average control for an application of dimethenamid alone was 88% (n = 3) at 14–41 DAA and 90% (n = 3) at 41 or more DAA. The level of control provided by dimethenamid for this grass weed was not compromised when tankmixed with Distinct®.

Yellow foxtail (*Setaria glauca*)
The following rationale has been submitted in support of the claim of control yellow foxtail with the Distinct® + dimethenamid tankmix:

- The submitted data indicates consistent control of yellow foxtail with the Distinct® + dimethenamid tankmix at other stages of application; and

- the submitted data indicates the control of annual grasses by dimethenamid is not compromised when tankmixed with Distinct®.

Based on the above, the claim of control for yellow foxtail with the Distinct® + dimethenamid tankmix is acceptable.

Crabgrass (*Digitaria sanguonalis*)
Control of crabgrass was reported in five trials conducted over one year over three locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 89% (n = 3) at 14–41 DAA and 88% (n = 2) at 41 or more DAA. The average control for an application of dimethenamid alone was 78% (n = 3) at 14–41 DAA and 87% (n = 2) at 41 or more DAA. The level of control provided by dimethenamid for this grass weed was not compromised when tankmixed with Distinct®.

Barnyard grass (*Echinochloa crusgalli*)
Control of barnyard grass was reported in six trials conducted over two years over four locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 98% (n = 3) at 14–41 DAA and 97% (n = 3) at 41 or more DAA. The average control for an application of dimethenamid alone was 91% (n = 3) at 14–41 DAA and 95% (n = 3) at 41 or more DAA. The level of control provided by dimethenamid for this grass weed was not compromised when tankmixed with Distinct®.

Fall panicum (*Panicum dichotomiflorum*)
Control of fall panicum was reported in two trials conducted over two years over two locations across Ontario and Quebec. The average control for an application of the Distinct® + dimethenamid tankmix was 93% (n = 2) at 14–41 DAA and 89% (n = 2) at 41 or more DAA. The average control for an application of dimethenamid alone was 84% (n = 2) at 14–41 DAA and 86% (n = 3) at 41 or more DAA. The level of control provided by dimethenamid for this grass weed was not compromised when tankmixed with Distinct®.

Old witchgrass (*Panicum capillare*)
Control of old witchgrass was reported in one trial conducted in Ontario. The control for an application of the Distinct® + dimethenamid tankmix was 99% (n = 1) at 14–41 DAA and 97% (n = 1) at 41 or more DAA. The average control for an application of dimethenamid alone was 91% (n = 1) at 14–41 DAA and 96% (n = 1) at 41 or more DAA. The level of control provided by dimethenamid for this grass weed was not compromised when tankmixed with Distinct®.

7.1.4.4 Late post-emergent application (4- to 6-leaf stage of the corn crop)

Distinct® at 0.200 kg a.i./ha alone

Redroot pigweed (*Amaranthus retroflexus*)
Control of redroot pigweed was reported in 17 trials conducted over two years over 11 locations across Ontario and Quebec. The average control for an application of Distinct® alone was 94% (n = 17) at 14–41 DAA and 96% (n = 12) at 41 or more DAA.

Lamb's-quarters (*Chenopodium album*)
Control of lamb's-quarters was reported in 19 trials conducted over two years over 13 locations across Ontario and Quebec. The average control for an application of Distinct® alone was 95% (n = 19) at 14–41 DAA and 98% (n = 15) at 41 or more DAA.

Common ragweed (*Ambrosia artemisiifolia*)
Control of common ragweed was reported in 10 trials conducted over two years over nine locations across Ontario and Quebec. The average control for an application of Distinct® alone was 98% (n = 9) at 14–41 DAA and 99% (n = 6) at 41 or more DAA.

Wild buckwheat (*Polygonum convolvulus*)
Control of wild buckwheat was reported in eight trials conducted over two years over four locations across Ontario and Quebec. The average control for an application of the Distinct® alone was 96% (n = 8) at 14–41 DAA and 98% (n = 6) at 41 or more DAA.

Lady's thumb (*Polygonum persicaria*)
Control of lady's thumb was reported in nine trials conducted over two years over six locations across Ontario and Quebec. The average control for an application of the Distinct® alone was 98% (n = 9) at 14–41 DAA and 99% (n = 6) at 41 or more DAA.

Velvetleaf (*Abutilon theophrasti*)
Control of velvetleaf was reported in four trials conducted over one year over four locations across Ontario and Quebec. The average control for an application of the Distinct® alone was 87% (n = 4) at 14–41 DAA and 96% (n = 3) at 41 or more DAA.

7.2 Effects on the yield of treated plants or plant products in terms of quantity and/or quantity

7.2.1 Pre-emergent application

Distinct® + dimethenamid
A total of seven trials were taken to yield and assessed for any yield effects on field corn when Distinct® was applied at the requested rate of 0.200 kg a.i./ha + dimethenamid in the presence of weeds. In addition, these seven trials tested Distinct® at 1.5× and 2× the requested rate. The rate of dimethenamid was a constant at 1.125 kg a.i./ha. The plots treated with the requested rate of Distinct® yielded 129% compared to the check. The plots treated with the 1.5× rate of Distinct® yielded 137% compared to the check. The plots treated with the 2× rate of Distinct® yielded 140% compared to the check.

7.2.2 Spike stage application (spike- to 1-leaf stage of the corn crop)

a) Distinct® alone

A total of two trials were taken to yield, and assessed for any yield effects on field corn when Distinct® was applied at the requested rate of 0.200 kg a.i./ha in the presence of weeds. In addition, these two trials tested Distinct® at the 1.5× and 2× rate. The plots treated with the requested rate of Distinct® yielded 106% compared to the check. The

plots treated with the 1.5× rate of Distinct® yielded 108% compared to the check. The plots treated with the 2× rate of Distinct® yielded 108% compared to the check.

b) Distinct® + dimethenamid

A total of four trials were taken to yield, and assessed for any yield effects on field corn when Distinct® was applied at the requested rate of 0.200 kg a.i./ha + dimethenamid in the presence of weeds. In addition, these four trials tested Distinct® at the 1.5× and 2× rate. The rate of dimethenamid was a constant at 1.125 kg a.i./ha. The plots treated with the requested rate of Distinct® yielded 171% compared to the check. The plots treated with the 1.5× rate of Distinct® yielded 175% compared to the check. The plots treated with the 2× rate of Distinct® yielded 170% compared to the check.

7.2.3 Early Post-emergent application (2- to 3-leaf stage of the corn crop)

a) Distinct® alone

A total of six trials were taken to yield, and assessed for any yield effects on field corn when Distinct® was applied at the requested rate of 0.200 kg a.i./ha in the presence of weeds. In addition, these six trials tested Distinct® at the 1.5× and 2× rate. The plots treated with the requested rate of Distinct® yielded 122% compared to the check. The plots treated with the 1.5× rate of Distinct® yielded 126% compared to the check. The plots treated with the 2× rate of Distinct® yielded 122% compared to the check.

b) Distinct® + dimethenamid

A total of one trial was taken to yield, and assessed for any yield effects on field corn when Distinct® was applied at the requested rate of 0.200 kg a.i./ha + dimethenamid in the presence of weeds. In addition, this trial tested Distinct® at the 1.5× and 2× rate. The rate of dimethenamid was a constant at 1.125 kg a.i./ha. The plots treated with the requested rate of Distinct® yielded 110% compared to the check. The plots treated with the 1.5× rate of Distinct® yielded 100% compared to the check. The plots treated with the 2× rate of Distinct® yielded 99% compared to the check.

7.2.4 Late Post-emergent application (4- to 6-leaf stage of the corn crop)

Distinct® alone

A total of seven trials were taken to yield, and assessed for any yield effects on field corn when Distinct® was applied at the requested rate of 0.200 kg a.i./ha in the presence of weeds. In addition, these seven trials tested Distinct® at the 1.5× and 2× rate. The plots treated with the requested rate of Distinct® yielded 131% compared to the check. The plots treated with the 1.5× rate of Distinct® yielded 124% compared to the check. The plots treated with the 2× rate of Distinct® yielded 120% compared to the check.

7.3 Phytotoxicity to target plants (including different cultivars), or to target plant products

7.3.1 Pre-emergent application

Distinct® + dimethenamid

Tolerance of field corn to the Distinct® + dimethenamid tankmix was evaluated in 14 trials conducted over a three-year period over 12 locations across Ontario and Quebec. Eight corn varieties were tested. The tankmix was tested at rates of Distinct® ranging from the proposed label rate of 0.200 kg a.i./ha up to 0.400 kg a.i./ha. The rate of dimethenamid was a constant at 1.125 kg a.i./ha. Data collected included visual evaluation of crop tolerance at 14–41 DAA and 41 or more DAA.

Distinct® at 0.200 kg a.i./ha + dimethenamid at 1.125 kg a.i./ha
Thirteen trials conducted over a three-year period reported an average of 0.4% (n = 12) visual injury at 14–41 DAA and 0.9% (n = 13) at 41 or more DAA.

Distinct® at 0.300 kg a.i./ha + dimethenamid at 1.125 kg a.i./ha (1.5×)
Thirteen trials conducted over a three-year period reported an average of 0.9% (n = 12) visual injury at 14–41 DAA and 1.2% (n = 13) at 41 or more DAA.

Distinct® at 0.400 kg a.i./ha + dimethenamid at 1.125 kg a.i./ha (2×)
Twelve trials conducted over a three-year period reported an average of 0.4% (n = 12) visual injury at 14–41 DAA and 1.1% (n = 1) at 41 or more DAA.

7.3.2 Spike stage application (spike- to 1-leaf stage of the corn crop)

a) Distinct® alone

Tolerance of field corn to Distinct® alone was evaluated in 13 trials conducted over a two-year period over 11 locations across Ontario and Quebec. Eight corn varieties were tested. Distinct® alone was tested at rates ranging from the proposed label rate of 0.200 kg a.i./ha up to 0.400 kg a.i./ha. Data collected included visual evaluation of crop tolerance at 14–41 DAA and 41 or more DAA.

Distinct® at 0.200 kg a.i./ha
Thirteen trials conducted over a two-year period reported an average of 0.3% (n = 13) visual injury at 14–41 DAA and 0% (n = 11) at 41 or more DAA.

Distinct® at 0.300 kg a.i./ha (1.5×)
Thirteen trials conducted over a two-year period reported an average of 0.8% (n = 13) visual injury at 14–41 DAA and 0.4% (n = 11) at 41 or more DAA.

Distinct® at 0.400 kg a.i./ha (2×)
Thirteen trials conducted over a two-year period reported an average of 0.7% (n = 13) visual injury at 14–41 DAA and 0.3% (n = 11) at 41 or more DAA.

b) Distinct® + dimethenamid

Tolerance of field corn to the Distinct® + dimethenamid tankmix was evaluated in 15 trials conducted over a three-year period over 11 locations across Ontario and Quebec. Eight corn varieties were tested. The tankmix was tested at rates of Distinct® ranging from the proposed label rate of 0.200 kg a.i./ha up to 0.400 kg a.i./ha. The rate of dimethenamid was a constant at 1.125 kg a.i./ha. Data collected included visual evaluation of crop tolerance at 14–41 DAA and 41 or more DAA.

Distinct® at 0.200 kg a.i./ha + dimethenamid at 1.125 kg a.i./ha
Fifteen trails conducted over a three-year period reported an average of 0.4% (n = 15) visual injury at 14–41 DAA and 0.3% (n = 13) at 41 or more DAA.

Distinct® at 0.300 kg a.i./ha + dimethenamid at 1.125 kg a.i./ha (1.5×)
Fifteen trails conducted over a three-year period reported an average of 1.1% (n = 15) visual injury at 14–41 DAA and 0.3% (n = 13) at 41 or more DAA.

Distinct® at 0.400 kg a.i./ha + dimethenamid at 1.125 kg a.i./ha (2×)
Fifteen trails conducted over a three-year period reported an average of 0.7% (n = 15) visual injury at 14–41 DAA and 0.4% (n = 13) at 41 or more DAA.

7.3.3 Early post-emergent application (2- to 3-leaf stage of the corn crop)

a) Distinct® alone

Tolerance of field corn to Distinct® alone was evaluated in 22 trials conducted over a two-year period over 13 locations across Ontario and Quebec. Ten corn varieties were tested. Distinct® alone was tested at rates ranging from the proposed label rate of 0.200 kg a.i./ha up to 0.400 kg a.i./ha. Data collected included visual evaluation of crop tolerance at 14–41 DAA and 41 or more DAA.

Distinct® at 0.200 kg a.i./ha
Twenty-two trials conducted over a two-year period reported an average of 1.0% (n = 21) visual injury at 14–41 DAA and 0.6% (n = 14) at 41 or more DAA.

Distinct® at 0.300 kg a.i./ha (1.5×)
Twenty-two trials conducted over a two-year period reported an average of 2.2% (n = 21) visual injury at 14–41 DAA and 2.0% (n = 14) at 41 or more DAA.

Distinct® at 0.400 kg a.i./ha (2×)
Twenty-two trials conducted over a two-year period reported an average of 2.3% (n = 21) visual injury at 14–41 DAA and 0.7% (n = 14) at 41 or more DAA.

b) Distinct® + dimethenamid

Tolerance of field corn to the Distinct® + dimethenamid tankmix was evaluated in nine trials conducted over a two-year period over eight locations across Ontario and Quebec. Six corn varieties were tested. The tankmix was tested at rates of Distinct® ranging from the proposed label rate of 0.200 kg a.i./ha up to 0.400 kg a.i./ha. The rate of dimethenamid was a constant at 1.125 kg a.i./ha. Data collected included visual evaluation of crop tolerance at 14–41 DAA and 41 or more DAA.

Distinct® at 0.200 kg a.i./ha + dimethenamid at 1.125 kg a.i./ha
Nine trials conducted over a two-year period reported an average of 1.4% (n = 9) visual injury at 14–41 DAA and 3.2% (n = 9) at 41 or more DAA.

Distinct® at 0.300 kg a.i./ha + dimethenamid at 1.125 kg a.i./ha (1.5×)
Nine trials conducted over a two-year period reported an average of 2.5% (n = 9) visual injury at 14–41 DAA and 4.6% (n = 9) at 41 or more DAA.

Distinct® at 0.400 kg a.i./ha + dimethenamid at 1.125 kg a.i./ha (2×)
Nine trials conducted over a two-year period reported an average of 3.4% (n = 9) visual injury at 14–41 DAA and 7.2 (n = 9) at 41 or more DAA.

7.3.4 Late post-emergent application (4- to 6-leaf stage of the corn crop)

Distinct® alone

Tolerance of field corn to the Distinct® alone was evaluated in 19 trials conducted over a two-year period over 14 locations across Ontario and Quebec. Eleven corn varieties were tested. Distinct® alone was tested at rates ranging from the proposed label rate of 0.200 kg a.i./ha up to 0.400 kg a.i./ha. Data collected included visual evaluation of crop tolerance at 14–41 DAA and 41 or more DAA.

Distinct® at 0.200 kg a.i./ha
Nineteen trials conducted over a two-year period reported an average of 3.0% (n = 19) visual injury at 14–41 DAA and 1.5% (n = 15) at 41 or more DAA.

Distinct® at 0.300 kg a.i./ha (1.5×)
Nineteen trials conducted over a two-year period reported an average of 4.5% (n = 19) visual injury at 14–41 DAA and 1.5% (n = 15) at 41 or more DAA.

Distinct® at 0.400 kg a.i./ha (2×)
Nineteen trials conducted over a two-year period reported an average of 5.6% (n = 19). visual injury at 14–41 DAA and 2.5% (n = 15) at 41 or more DAA.

7.4 Observations on undesirable or unintended side effects

7.4.1 Impact on succeeding crops

No crop restrictions are required with the maximum rate of Distinct®.

7.5 Conclusions

The data provided indicates that, when used according to label directions, Distinct® can be applied to field corn for the control of specific broadleaf weeds. Distinct® may be tankmixed with dimethenamid to provide additional annual grass control.

7.5.1 Summary

Table 7.3 Summary

Crop	Field Corn
Application timing	1.Pre-emerge 2. Spike stage (spike- to 1-leaf) 3. Early post-emergent (2- to 3-leaf) 4. Late post-emergent (4- to 6-leaf) application
Product **Rate of application** **PLUS** **Additional surfactant**	Distinct® 285 g/ha for post-emerge applications - non-ionic surfactant at 0.25% v/v - liquid urea ammonium nitrate at 1.25% v/v
Weed species controlled	redroot pigweed, common ragweed, lamb's-quarters, wild buckwheat, lady's thumb and velvetleaf (velvetleaf controlled with post-emergent application only).
Tankmix option	dimethenamid

8.0 Overall Conclusion

Distinct® provides commercially acceptable crop tolerance to field corn when applied at 285 g/ha. Distinct® will control redroot pigweed, common ragweed, lamb's-quarters, wild buckwheat, lady's thumb and velvetleaf (velvetleaf controlled with post-emergent application only). Distinct® may be tankmixed with dimethenamid for control of specific annual grass weeds.

Short-term dermal and dietary toxicology studies were deemed most appropriate for use in occupational risk assessment. Calculated margins of exposure were adequate for farmers and custom applicators. From the perspective of occupational exposure, the product is be supported.

The precautionary label statement was modified to include:

"When mixing and loading or applying, wear a long-sleeved shirt, long pants, shoes and socks. In addition, wear chemical-resistant gloves and protective eyewear (face shield or safety glasses) while mixing and loading."

"Do not re-enter treated areas within 12 hours."

Based on the results of acute toxicity testing, the words "CAUTION POISON", "CAUTION EYE IRRITANT" and "POTENTIAL SKIN SENSITIZER" are displayed on the primary panel of the label.

The plant metabolism studies demonstrated that diflufenzopyr degraded rapidly. No parent compound was detected in corn commodities. Most TRRs were found in corn silage and fodder. Since diflufenzopyr degraded rapidly to M1, for registration purposes, the ROC is defined as the parent compound and its metabolites convertible to M1.

The results of the supervised trial conducted in Eastern Canada indicated that when field corn was treated with diflufenzopyr according to the proposed label directions, no residue (<0.02 ppm) were detected at harvest in corn commodities.

The proposed analytical method for diflufenzopyr residues involved converting the parent compound to M1. Quantification was performed by GC/NPD or GC/MSD. The LOQ of this method was 0.01 ppm M1 (0.02 ppm diflufenzopyr equivalent). Since the molecular weight of M1 is roughly half of the parent compound, the concentrations of M1 determined must be doubled when expressed in diflufenzopyr equivalents.

The EPA proposed a tolerance of 0.05 ppm in corn grain, forage and fodder. To harmonize with U.S. tolerance, the PMRA proposes a MRL of 0.05 ppm for corn grain.

The animal metabolism studies showed that over 90% of diflufenzopyr in diet was excreted. The anticipated residue levels in treated corn commodities were under the LOQ. The TRRs in all edible livestock commodities were ≤0.0005 ppm (0.5 ppb) when extrapolated from the 200× feeding level to the anticipated 1× feeding level; therefore, an animal feeding study was not required. Maximum residue limits would not be needed for meat, milk and eggs.

Metabolism studies indicated that there were no significant novel corn plant metabolites when compared to goat, hen or rat metabolic profiles.

Potential exposure to diflufenzopyr in the diet is very low. If a proposed MRL of 0.05 ppm is used for corn grain, and 0.1 ppm general regulation level is used for animal tissues, which is highly exaggerated, the PDI for adults, infants and children will all be below 4% of the ADI allotted to food. Ten percent of the ADI is allotted to drinking water.

Based on discussions with the EPA, the applicant was requested to submit the following studies.

- An additional terrestrial field study that has been conducted in the corn-growing region of Ontario or in a state in the Northern U.S. that has similar soil and climatic conditions to that region.

- Vegetative vigour studies with Distinct® and the technical active ingredient.

The EPA will request additional studies in accordance with their requirements.

List of Abbreviations

A.E.	acid equivalent
a.i.	active ingredient
AD	administered dose
ADI	acceptable daily intake
ARfD	acute reference dose
bw	body weight
CAS	Chemical Abstracts Service
d	day
DAA	days after application
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
DT_{50}	decline time
dw	dry weight
EC_{50}	effect concentration
EEC	expected environmental concentration
EPA	Environmental Protection Agency
GC	gas chromatography
GSD	geometrical standard deviation
h	hour
HPLC	high performance liquid chromatography
IAA	indoleacetic acid
K_{oc}	adsorption constant
K_{ow}	octanol/water partition coefficient
LC	liquid chromatography
LC_{50}	Lethal Concentration 50%
LD_{50}	Lethal Dose 50%
LOQ	limit of quantitation
M1	8-methyl-5-hydroxy-pyrido(2,3-d)-pyridazine (phthalazinone)
M2	3,5-difluoroaniline (aniline)
M5	6-((3,5-difluorophenyl) carbamoyl)-8-methyl-pyrido (2,3-d)-5-pyridazinone (carbamoyl phthalazinone)
M6	2-acetyl nicotinic acid (3,5-difluoroaniline)
M8	methyl N-(3,5-difluorophenyl)carbamate
M9	8-methylpyrido[2,3-d]pyridazine-2,5(1H, 6H)-dione (2-keto-M1)
M10	8-hydroxymethyl-5(6H)-pyrido[2,3-d]pyridazinone (8-hydroxymethyl-M1)
M19	8-hydroxymethylpyrido[2,3-d]pyridazine-2,5(1H,6H)-dione
M20	glucoside of M19
MCHC	mean corpuscular hemaglobin concentration
MCV	mean corpuscular volume
MMAD	mass median aerodynamic diameter
MPCE	micronucleated polychromatic erythrocytes
MRL	maximum residue limit
MS	mass spectrometry
MSD	mass selective detection

n	number of trials
NAFTA	North American Free Trade Agreement
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NPD	nitrogen-phosphorus detector
NZW	New Zealand White
PDI	potential daily intake
PHED	Pesticide Handler Exposure Database
pK_a	dissociation constant
PMRA	Pest Management Regulatory Agency
ppm	parts per million
PWDH	Pirbright White Dunkin Hartley
RAC	raw agricultural commodity
ROC	residue of concern
SD	Sprague Dawley
SF	safety factor
TGAI	technical grade active ingredient
TLC	thin-layer chromatography
TRR	total radioactive residue
U.S.	United States
v/v	volume ratio
yr	year

Appendix I

Summary table of toxicology studies for diflufenzopyr

Metabolism - technical (diflufenzopyr)

Male and female Wistar rats received either a single low intravenous dose (1.0 mg/kg bw), single low oral dose (10.0 mg/kg bw), single high oral dose (1000 mg/kg bw) or 15 daily low oral doses (10.0 mg/kg bw) of diflufenzopyr, purity >98%, 10 or 15 rats per sex per group. Diflufenzopyr was radiolabelled as [phenyl-U- ^{14}C] or [pyridinyl-4, 6-^{14}C]. Prior to dosing, five rats per sex in all but the repeat dose group were bile-duct cannulated, and sacrificed 48 h post-dosing. Of the remaining 10 rats per sex in each group (i.e., non-cannulated), five per sex per group were sacrificed 24 h post-dosing, and the remaining five per sex per group were sacrificed 72 h post-dosing.

After oral administration, a smaller percentage of the administered dose (AD) was excreted in the urine (20–44%) and more in the feces (49–79%), when compared to intravenous administration (61–89% in the urine), indicating that diflufenzopyr was only partially absorbed following oral dosing. Sex, dose level and pre-treatment had little effect on the excretion pattern. Three- to 19% of the AD was recovered in the bile of all dose groups, indicating that enterohepatic circulation played a role in the elimination of diflufenzopyr. The approximate half-life of diflufenzopyr was 5.3–6.9 h for all single oral and intravenous dose groups, and 7.7–10.8 h for the repeat oral dose group.

Diflufenzopyr did not accumulate in the tissues; total radioactive residues (TRRs) accounted for <3% of the AD for all dose groups. Residue levels were highest in blood, red blood cells and serum for the phenyl-labelled groups, and highest in liver and kidney for the pyridinyl-labelled groups.

The major fraction of TRR extracted from urine, feces and bile was identified as unchanged diflufenzopyr. In addition, minor amounts of hydrolysis products [i.e., 8-methyl-5-hydroxy-pyrido(2,3-d)-pyridazine (M1); 6-((3,5-difluorophenyl)carbamoyl)-8-methyl-pyrido(2,3-d)-5-pyridazinone (M5); and 2-acetyl nicotinic acid (M6)] and hydroxylation products [i.e., 8-methylpyrido[2,3-d]pyridazine-2,5(1H,6H)-dione (M9); 8-hydroxymethyl-5(6H)-pyrido[2,3-d]pyridazinone (M10); and 8-hydroxymethylpyrido[2,3-d]pyridazine-2,5(1H,6H)-dione (M19)] were identified in excreta.

Study	Species/strain and doses	NOEL/NOAEL mg/kg bw/d	Target organ/significant effects/comments
Acute studies - technical (diflufenzopyr)			
Oral	Rat, SD, 5/sex, 5000 mg/kg bw	LD_{50} >5000 mg/kg bw	Clinical observations consisted of piloerection, pallor, hunched posture and liquid feces. Low Toxicity.
Dermal	Rabbit, SD, 5/sex, 5000 mg/kg bw	LD_{50} >5000 mg/kg bw	Slight- to well-defined erythema was noted on all rabbits, recovery by day 9. Low Toxicity
Inhalation	Rat, SD, 5/sex, 2.93 mg/L	LC_{50} >2.93 mg/L	Mass median aerodynamic diameter (MMAD) = 3.5 µm, geometrical standard deviation GSD = 2.2 77% <7 µm; 36% <3.5µm No clinical signs of toxicity. Low Toxicity.

Study	Species/strain and doses	NOEL/NOAEL mg/kg bw/d	Target organ/significant effects/comments
Skin Irritation	Rabbit, NZW, six males, 0.5 g dose	PIS = 0.00	Non-irritating.
Eye Irritation	Rabbit, NZW, six males, 0.1 mL dose (30 mg)	MAS = 7.3	Minimally irritating.
Skin Sensitization (Modified Buehler method)	Guinea pig, Pirbright White Dunkin Hartley. Test material administered: 60% (0.5 g) for induction; and 50% (0.5 g) for challenge. Positive control reference data with alpha-hexlycinnamaldehyde 85%.	Test material was minimally irritating at 60% concentration. No evidence of sensitization. Positive control was sensitizing, demonstrating responsiveness of assay.	Not a sensitizer.
Acute studies - formulation (Distinct®)			
Oral	Rat, SD, 5/sex, 1260, 2000 and 3200 mg/kg bw	LD_{50} (mg/kg bw): Males: 1600 (1200–2100) Females: 2100 (1600–2800) Combined: 1800 (1500–2200)	Clinical observations consisted of piloerection, unsteadiness, delayed reflex, lethargy, pallor, hunched posture, abnormal gait, prostration, increased salivation and red/brown staining of mouth and nose. Slight toxicity. Label Recommendation: "CAUTION POISON"
Dermal	Rabbit, SD, 5/sex, 5000 mg/kg bw	LD_{50} >5000 mg/kg bw	Slight- to well-defined erythema and edema was noted on all rabbits, recovery between days 10 and 14 for edema; erythema persisted to day 14. Desquamation, all rabbits, days 4–14. Low toxicity.
Inhalation	Rat, SD, 5/sex, 2.93 mg/L	LC_{50} >5.34 mg/L	MMAD = 3.5 µm, GSD = 2.3. Wet fur on snout and facial brown staining, days 0 and 1. Low toxicity.
Skin Irritation	Rabbit, NZW, six males, 0.5 g dose	PIS = 1.5	Slightly irritating.
Eye Irritation	Rabbit, NZW, six males, 0.1 mL dose (30 mg)	MAS = 19.7	Mildly irritating. Label recommendation: "CAUTION EYE IRRITANT"

Study	Species/strain and doses	NOEL/NOAEL mg/kg bw/d	Target organ/significant effects/comments
Skin Sensitization (Modified Buehler method)	Guinea pig, Pirbright White Dunkin Hartley. Test material administered: 40% (0.5 g) for induction; 20% (0.5 g) for challenge. Positive control reference data with alpha-hexylcinnamaldehyde 85%.	Test material was minimally irritating at 40% concentration. Positive skin reaction in 95% of the test animals after challenge. Positive control was sensitizing, demonstrating responsiveness of assay.	Skin sensitizer. Label recommendation: "POTENTIAL SKIN SENSITIZER"
Short term - technical (diflufenzopyr)			
21- to 24-d dermal	Rabbits, NZW, 5/sex/group, 0, 100, 300 and 1000 mg/kg bw/d	NOEL = 1000 mg/kg bw/d	No systemic treatment-related effects at any dose level tested. Local dermal irritation was observed at all dose levels tested.
90-d dietary	Mouse, CD-1, 10/sex/group, 0, 350, 1750, 3500 and 7000 ppm (equal to 0, 58, 287, 613 and 1225 mg/kg bw/d for males, and 0, 84, 369, 787 and 1605 mg/kg bw/d for females)	NOEL = 7000 ppm (1225 mg/kg bw/d for males, and 1605 mg/kg bw/d for females)	No treatment-related effects at any dose level tested.
90-d dietary	Rat, Wistar, 10/sex/group, 0, 1000, 5000, 10,000 and 20,000 ppm (equal to 0, 60.8, 352, 725 and 1513 mg/kg bw/d for males, and 0, 72.8, 431, 890 and 1750 mg/kg bw/d for females). An additional 10/sex were assigned to the 0- and 20,000-ppm groups for a four-week recovery period.	NOEL = 5000 ppm (352 mg/kg bw/d for males, and 431 mg/kg bw/d for females)	10,000 and 20,000 ppm: Lower body weight gain and decreased food efficiency; increased incidence of foamy macrophages in the lungs. 20,000 ppm: Increased incidence of testicular atrophy. After the four-week recovery period, foamy macrophages in the lungs and testicular atrophy were still evident at 20,000 ppm.

Study	Species/strain and doses	NOEL/NOAEL mg/kg bw/d	Target organ/significant effects/comments
90-d dietary	Dog, beagle, 4/sex/group, 0, 1500, 10,000 and 30,000 ppm (equal to 0, 58, 403 and 1121 mg/kg bw/d for males, and 0, 59, 424 and 1172 mg/kg bw/d for females)	NOEL = 1500 ppm (58 mg/kg bw/d)	10,000 and 30,000 ppm: Erythroid hyperplasia in the bone marrow; extramedullary hematopoiesis in the liver; and hemosiderin deposits in Kupffer cells. 30,000 ppm: Lower body weight gain and food consumption; regenerative anemia; extramedullary hematopoiesis in the lungs, lymph nodes and kidneys; absence of fatty bone marrow; urothelial hyperplasia and cystitis.
52-wk dietary	Dog, beagle, 4/sex/group, 0, 750, 7500 and 15,000 ppm (equal to 0, 26, 299 and 529 mg/kg bw/d for males, and 0, 28, 301 and 538 mg/kg bw/d for females)	NOEL = 750 ppm (26 mg/kg bw/d)	7500 and 15,000 ppm: Erythroid hyperplasia in the bone marrow; hemosiderin deposits in the kidneys, liver and spleen; reticulocytosis; lower body weight gain and decreased food utilization (females only).
Short term - formulation (Distinct®)			
21- to 24-d dermal	Rabbits, NZW, 5/sex/group, 0, 10, 30 and 100 mg/kg bw/d	NOEL = 100 mg/kg bw/d	No systemic treatment-related effects at any dose level tested. Local dermal irritation was observed at all dose levels tested.
Chronic toxicity/oncogenicity - technical (diflufenzopyr)			
78-week dietary	Mouse, CD-1, 60/sex/group, 0, 700, 3500 and 7000 ppm (equal to 0, 100, 517 and 1037 mg/kg bw/d for males, and 0, 98, 500 and 1004 mg/kg bw/d for females)	Chronic Effects: Males, NOEL = 7000 ppm (1037 mg/kg bw/d) Females, NOAEL = 7000 (1004 mg/kg bw/d) Oncogenicity: NOEL = 7000 ppm (1037 mg/kg bw/d for males, and 1004 mg/kg bw/d for females)	For males: No treatment-related findings at any dose level tested. For females, at 7000 ppm: Slightly lower body weight gain during the second year of the study. No treatment-related oncogenic effects at any dose level tested.

Study	Species/strain and doses	NOEL/NOAEL mg/kg bw/d	Target organ/significant effects/comments
104-week dietary	Rat, Wistar, 72/sex/group, 0, 500, 1500, 5000 and 10,000 ppm (equal to 0, 22, 69, 236 and 518 mg/kg bw/d for males, and 0, 29, 93, 323 and 697 mg/kg bw/d for females)	Chronic Effects: NOAEL = 5000 ppm (236 mg/kg bw/d for males, and 323 mg/kg bw/d for females) Oncogenicity: NOEL = 10,000 ppm (518 mg/kg bw/d for males and 697 mg/kg bw/d for females)	1500 and 5000 ppm: Slightly lower body weight gain during the second year of the study (only attaining a maximum 10% reduction; non-adverse). 10,000 ppm: Lower body weight gain throughout the study period. No treatment-related oncogenic effects at any dose level.
Reproduction/developmental toxicity - technical (diflufenzopyr)			
Two-generation dietary, two litters in the P generation, one litter in the F_1 generation	Rat, SD, 26/sex/group, 0, 500, 2000 and 8000 ppm (equal to 0, 27.3, 113.1 and 466.2 mg/kg bw/d for males, and 0, 42.2, 175.9 and 742.0 mg/kg bw/d for females)	Systemic Effects: NOAEL = 2000 ppm (113.1 mg/kg bw/d for males and 175.9 mg/kg bw/d for females) Reproductive Effects: NOEL = 2000 ppm (113.1 mg/kg bw/d for males, and 175.9 mg/kg bw/d for females)	2000 ppm: Slightly lower body weight gain, P males during premating only. 8000 ppm: Lower body weight gain and increased food consumption, P and F generation during premating, both sexes; F and P generation females during gestation. 2000 and 8000 ppm: Slightly higher seminal vesicle weight, non-adverse in the absence of any related gross or histopathological findings. 8000 ppm: Lower body weight gain (F_1a); lower live birth and viability indices, and increased pre-perinatal loss (F_2 generation); increased number of runts (F_1a and F_1b).
Teratogenicity, oral gavage	Rat, SD, 25/group, 0, 100, 300 and 1000 mg/kg bw/d	Maternal NOAEL = 1000 mg/kg bw/d Developmental NOAEL = 1000 mg/kg bw/d	1000 mg/kg bw/d: Slightly lower body weight gain during the first three days of dosing only (not statistically significant). 1000 mg/kg bw/d: Increased incidence of incompletely ossified and/or unossified sternal centra. No teratogenic effects noted at any dose level tested.

Study	Species/strain and doses	NOEL/NOAEL mg/kg bw/d	Target organ/significant effects/comments
Teratogenicity, oral gavage	Rabbit, NZW, 20/group, 0, 30, 100 and 300 mg/kg bw/d	Maternal NOEL = 100 mg/kg bw/d Developmental NOEL = 100 mg/kg bw/d	300 mg/kg bw/d: Mortality; abortions; weight loss and lower food consumption during the dosing period; and abnormal feces. 300 mg/kg bw/d: Increased incidence of abortions. No teratogenic effects noted at any dose level tested.
Mutagenicity - technical (diflufenzopyr)			
Study	**Species/strain or cell type**	**Doses employed**	**Significant effects/comments**
Salmonella/ Ames Test	*S. typhimurium* - TA 98, TA 100, TA 1535, TA 1537 and TA 1538	0, 333, 667, 1000, 3330, 6670 and 10,000 µg/plate, ± S9	Negative
Forward cell mutation assay, in vitro	Cultured L5178Y (TK+/-) mouse lymphoma cells	0.05, 0.1, 0.5, 0.8, 1.0, 1.2, 1.4, 1.5, 1.6, 1.8, 2.0 and 3.0 mg/mL, ± S9	Negative
Cytogenetic assay, in vitro	Cultured human lymphocytes	100, 250, 500, 750 and 1000 µg/mL.	Negative
Unscheduled DNA synthesis assay, in vitro	Rat hepatocytes	0, 5.0, 10.0, 25.0, 50.0, 100 and 250 µg/mL, ± S9	Negative
Mammalian cytogenetics (micronucleus) assay, in vivo	Mouse, ICR	0, 500, 1667 and 5000 mg/kg bw, with sacrifice at 24, 48 and 72 h after dosing	Negative
Neurotoxicity - technical (diflufenzopyr)			
Acute oral gavage	Rat, Crl:CD BR, 10/sex/group, 0, 125, 500 and 2000 mg/kg bw	NOEL = 2000 mg/kg bw	No treatment-related effects were noted at any dose level tested.
13-week feeding study	Rat, Crl:CD BR, 10/sex/group, 0, 25, 75 and 1000 mg/kg bw/d	NOEL = 75 mg/kg bw/d	1000 mg/kg bw/d: Lower body weight gain and lower feed efficiency. No treatment-related neurotoxic effects were noted at any dose level tested.
Recommendation for ADI: 0.26 mg/kg bw/d, based on the lowest NOEL of 26 mg/kg bw/d in the chronic rat study, and using a 100-fold safety factor. Recommendation for ARfD: 1.00 mg/kg bw/d, based on the NOEL of 100 mg/kg bw/day in the rabbit teratology study, and using a 100-fold safety factor.			